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(54) Title: IN SILICO SCREENING FOR PHENOTYPE-ASSOCIATED EXPRESSED SEQUENCES

(57) Abstract: The present invention provides methods for determining whether a nucleic acid sequence is a marker for a phenotype or cell type of interest which comprises providing a database of expressed sequence tag sequences (EST's) from the species; placing said EST's in groups termed clusters based on homology of EST's within each cluster; determining for each cluster the total number of EST"s within said cluster; ordering said clusters sequentially based on the number of EST's in each cluster; dividing said ordered clusters into subranges based on the number of EST's per cluster; determining for each cluster subrange obtained from step (e) the number EST's within said cluster which are expressed in said predetermined cell type of interest; calculating according to a normal distribution the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in said cell type of interest, wherein said threshold percentage is a percentage from about 10% to about 100%; determining the number of clusters in each subrange observed to contain said predetermined threshold percentage of EST's expressed in said predetermined cell type; and identifying subranges having an observed number of clusters that meet said predetermined threshold percentage greater than the number of clusters expected to meet said predetermined threshold percentage for the subrange according to normal distribution; wherein if the percentage of EST's expressed in said cell type of interest in a cluster identified is equal to or greater than said predetermined threshold percentage, the cluster contains a nucleic acid that is a marker for the cell type of interest.

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IN SILICO SCREENING FOR PHENOTYPE-ASSOCIATED EXPRESSED SEQUENCES

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FIELD OF THE INVENTION

[0001] The present application is related to, and claims the benefit of priority of, Provisional Application No.'s 60/293,999, filed May 30, 2001, 60/330,457, filed October 22, 2001, and 60/357,144, filed February 19, 2002, all of which are incorporated in their entirety by reference herein.

[0002] The invention relates generally to the field of genetics and differential expression of genes of interest. More specifically, the invention relates to methods for detecting expression of nucleic acids or proteins associated with a particular phenotype by performing a differential global comparison of a group of Expressed Sequence Tags (EST's) expressed in a particular tissue or cell type with a larger group of available EST's for a plurality of cell types.

[0003] The publications and other materials used herein to illuminate the background of the invention or provide additional details respecting the practice are incorporated by reference.

BACKGROUND OF THE INVENTION

- [0004] Comparing patterns of gene expression in different cell lines and tissues has important applications for a variety of biological problems. Such information is useful, for example, in comparing mechanisms of differentiation, microbial pathogenesis or tumor malignancy. Typically, such information is obtained by detecting altered gene or protein expression patterns associated with a particular phenotype. Comparing patterns of expression is particularly important, for example, in determining pattern(s) of expression that lead to aberrant cell growth, especially in tumor formation and cancer. A number of experimental methods have been designed for the detection of phenotype or celltype associated gene expression. Most of them are based on time-consuming and expensive experimental protocols (e.g., numerous modifications of the differential display approach, cDNA microarrays, or Serial Analysis of Gene Expression).
- 30 [0005] EST's are an integral tool in the study of differential expression patterns. The total number of human ESTs in publicly available databases (>4 x10⁶) exceeds by approximately two orders of magnitude the total number of different transcripts that can be deduced from the number of human genes (2.5 4 x10⁴). Accordingly, there presently exists a need for computer-based

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procedures for the detection of EST expression profiles to replace traditional experimental protocols utilized in gene expression profiling.

[0006] UniGene is an experimental system for automatically partitioning GenBank sequences into a non-redundant set of gene-oriented EST clusters based on DNA sequence homology. Each UniGene cluster contains homologous or similar sequences that represent a unique "gene" or RNA transcript, as well as related information, such as the tissue type(s) in which expression of the transcript has been detected and the map location of the gene encoding the transcript. In addition to sequences of well-characterized genes, hundreds of thousands of novel EST's are also included in the UniGene partitioning system. Clustering is the process of finding subsets of sequences which belong together within a larger set. This is done by converting discrete similarity scores to boolean links between sequences using techniques well known in the art. That is, two sequences are considered linked if their similarity or homology exceeds a threshold. Sequence pairs which are sufficiently similar are linked together to form initial clusters. The set of ESTs is compared with the set of genes using the "megablast" algorithm (Zhang et al., J Comput Biol;7(1-2):203-14 (2000)) and sufficiently similar sequence pairs are added to a particular cluster. A detailed description of clustering performed in the UniGene system can be found at http//www.ncbi.nlm.nih.gov/UniGene.

[0007] Differentially expressed EST clusters may be useful as phenotypic markers and prognostic indicators and may be suitable targets for various therapeutic interventions. Prior art methods for the detection of phenotype or cell type of interest or expression patterns have included pairwise comparison of expression patterns in a the phenotype or cell type of interest and corresponding normal tissue in order to determine transcripts which are expressed either specifically or in higher quantities in the cell type of interest. As an example, such pairwise comparisons have been done for tumor-associated expression patterns.

[0008] The technique of computer based differential display (CDD) compares expression patterns in a particular tissue versus another tissue source. The comparison can be based on sequence databases available in the World Wide Web. This technique has been used to identify prostate-associated genes (Vasmatzis et al. Proc.Natl. Acad. Sci. USA 95, 300-304 (1998)) or ectopically expressed genes in particular tumor types in comparison to corresponding normal tissue (Schuerle et al. Cancer Res. 60, 4037-4043 (2000)).

[0009] There presently exists a need to develop computer based methods for comparing

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large numbers of EST's in a global fashion with all known phenotype-associated EST's, so that phenotype-associated patterns of gene expression can be culled from the massive number of such sequences available, without the need for an extensive number of microarray analyses or serial analyses of gene expression in a pairwise manner between a cell type of interest and another individual cell type.

SUMMARY OF THE INVENTION

[00010] The present invention provides methods for the detection of nucleic acid markers associated with a cell type or phenotype of interest by performing a global comparison of a group of EST's known to be expressed in the cell type or phenotype of interest with all EST's expressed in normal tissue in order to identify EST's that are preferentially expressed in the cell or phenotype of interest. The methods comprise arranging both the EST's of interest from a particular species and a larger group of other EST's available for the species in clusters based on homology among the EST's. The methods further comprise arranging the clusters into distinct subranges based on the number of EST's in each cluster and, based on the percentage of EST's derived from the cell type of interest, calculating the number of clusters expected to contain a predetermined percentage of EST's from the cell type of interest. Subranges which contain more than the expected number of clusters containing at least or more than the predetermined percentage of EST's from the cell type are selected for further analysis. The present invention also presents a method for determining a computer based differential display (CDD) of cell or phenotype-associated genes. In one embodiment, the cell or phenotype associated markers are determined for a tumor cell. In a preferred embodiment, at least some of the discrete steps in the method are performed on a computer and comparisons are made between global expression patterns of EST's in a specific cell type or phenotype (such as, e.g, tumor) versus global expression patterns of EST's in all other tissue. Alternatively, the comparisons can be made between EST's expressed in a specific cell type and EST's expressed in normal tissue. The approach was inspired by the hypothesis that evolutionary selective pressures might provide conditions for expression of genes that are not expressed in normal tissue (Kozlov, Medical Hypotheses 46, 81-84 (1996)). [00011]

[00011] In one embodiment, the invention provides methods for the detection of phenotype or cell type-associated markers by global comparison of all phenotype or cell type-associated EST's with all known EST's to identify EST's that are preferentially expressed in cells expressing the

particular phenotype. In a particularly preferred embodiment, the phenotype is tumor formation and the cell type is a tumor cell. Thus, in one embodiment, the invention provides a method for the detection of tumor markers by global comparison of all tumor associated EST's with all known EST's to identify EST's that are preferentially expressed in tumors.

[00012] In another embodiment, the invention provides a method for the detection of stress-related genes in a plant model relevant to agricultural plants. Thus, in another preferred embodiment, comparisons are made between global expression patterns of EST's in *Arabidopsis thaliana* grown in stress conditions (i.e., drought, cold, high salt concentration) versus global expression patterns of EST's in *A. thaliana* cultivated under normal conditions. Comparisons can also be made between mature plant cells and cells from roots or shoots.

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[00013] Analysis of combined preparations of mRNAs from several tissues in saturation and experimental subtractive hybridization procedures indicate that tumors contain more diverse sets of mRNAs than any normal tissue. This observation led to the idea of subtracting all available normal EST's (instead of pairwise comparisons) from all available tumor and corresponding normal tissue. (Evtushenko et al. Mol.Biol. 23, 510-520 (1989).

[00014] In one embodiment, the invention provides a method for determining whether a nucleic acid sequence is a marker preferentially expressed in a phenotype or cell type of interest from a biological species. In a preferred embodiment, the invention is performed with the aid of statistical software analysis and one or more computers and comprises the following steps: (a) providing a database of expressed sequence tag sequences (EST's); (b) placing said EST's in groups termed clusters based on homology of EST's within each cluster; (c) determining for each cluster the total number of EST"s within said cluster; (d) ordering said clusters sequentially based on the number of EST's in each cluster; (e) dividing said ordered clusters into subranges based on the number of EST's per cluster; (f) determining for each cluster subrange obtained from previous step (e) the number EST's within said cluster which are expressed in said predetermined cell type of interest; (g) calculating according to a normal distribution the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in said cell type of interest, wherein said threshold percentage is a percentage from about 10% to about 100%; (h) determining the number of clusters in each subrange observed to contain said predetermined threshold percentage of EST's expressed in said predetermined cell type; and (i) identifying subranges having an observed number of clusters that meet said predetermined threshold percentage greater than the

number of clusters expected to meet said predetermined threshold for the subrange according to normal distribution; wherein if the percentage of EST's expressed in said cell type of interest in a cluster identified in (i) is equal to or greater than said predetermined threshold percentage, said cluster contains a nucleic acid marker preferentially expressed in the cell type of interest. In preferred embodiments, the clusters of the invention are derived from the UniGene database, which contains all sequences associated with a cluster. The clusters have unique "Hs." Unigene cluster ID numbers to identify the cluster based on homology. Thus, once a cluster is identified as associated with a phenotype using the EST's from the cluster, the cluster-identifier can be used to identify all other sequences associated with the cluster such as full length mRNA's that are homologous to the EST's in the cluster. In this manner, a reference nucleic acid or polypeptide sequence for the cluster can be determined by reviewing the Unigen database. The methods of the present invention can be used with any database, as long as the database contains sequences that can be arranged in clusters based on homology.

[00015] In one embodiment, the invention provides a method for determining whether a nucleic acid is a marker in humans preferentially expressed in a tumor cell. In this embodiment, EST's from a database containing human EST's which contain a description of the source of the EST's retrieved from the cluster description are provided and arranged in individual clusters based on homology; for each cluster the total number of EST"s within said cluster is determined; said clusters are ordered sequentially based on the number of EST's in each cluster; said ordered clusters are divided into subranges based on the number of EST's per cluster; the number of EST's within said cluster which are expressed in tumors is determined for each cluster subrange; there is then calculated according to a normal distribution the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in tumors, wherein said threshold percentage is a percentage from about 90% to about 100%; the number of clusters is determined in each subrange observed to contain said predetermined threshold percentage of EST's expressed in tumors; and subranges having an observed number of clusters that meet said predetermined threshold percentage greater than the number of clusters expected to meet said predetermined threshold for the subrange according to normal distribution are identified; wherein if the percentage of EST's expressed in said cell type of interest in a cluster from a subrange identified as having a greater than expected number of such clusters is equal to or greater than said predetermined threshold percentage, said cluster contains a nucleic acid marker preferentially expressed in tumors.

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[00016] In another embodiment, the invention provides a method for detecting EST expression in stress induced A. thaliana which comprises the following steps: (a) for all individual A. thaliana EST clusters, the number of ESTs is retrieved from the cluster description; (b) next, the number of ESTs from all stress-induced cDNA libraries present in each cluster description is counted; (c) there is then determined for each cluster the total number of EST"s within said cluster; (d) said clusters are ordered sequentially based on the number of EST's in each cluster; (e) said ordered clusters are then divided into subranges based on the number of EST's per cluster, (f) it is then determined for each cluster subrange obtained from previous step (e) the number of EST's within said cluster which are expressed in Arabidopsis cells presented with stress conditions; (g) there is then calculated according to a normal distribution the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in said cell type of interest, wherein said threshold percentage is a percentage from about 10% to about 100%; (h) the number of clusters in each subrange observed to contain said predetermined threshold percentage of EST's expressed in said predetermined cell type is determined; and (i) subranges having an observed number of clusters that meet said predetermined threshold percentage greater than the number of clusters expected to meet said predetermined threshold for the subrange according to normal distribution are identified; wherein if the percentage of EST's expressed in stress-induced plants in a cluster identified in (i) is equal to or greater than said predetermined threshold percentage, said cluster contains a nucleic acid marker preferentially expressed in the stressinduced plants.

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[00017] The invention thus provides a method for correlating EST expression with a phenotype and in one embodiment requires correlation between a central unit or units containing EST sequence information. In a preferred embodiment, at least some of the EST sequence information analysis is implemented on a conventional personal computer, with the correlator being embodied in a software program. Because the correlator is embodied in software, it may be transported among various computers, which may be used separately or together to perform some or all of the various operations discussed herein.

[00018] In another embodiment, the invention provides a method for identifying a tumor cell which comprises detecting the expression of a tumor-associated marker of the present invention. As discussed in greater detail *infra*, the tumor-associated marker can be a nucleic acid or a polypeptide or fragments thereof.

[00019] In another embodiment, the invention provides a method for detecting a tumor cell by detecting the expression of nucleic acid sequences which are tumor-associated and can be used as diagnostic tools for the detection of tumor tissue. The tumor-associated nucleic acids are detected using the methods for determining whether a nucleic acid sequence is a marker for tumors as described herein. The sequences may be utilized for both in vitro and in vivo screening for the presence of a tumor cell. In one embodiment, the invention provides a method for detecting the expression of a tumor-associated nucleic acid sequence wherein the sequence is selected from the group consisting of SEQ ID NO:'s 9, 11, 13, 15, 17, 19, 23, 25, 27, 29, 33, 35, 37, 39, 41, 45, 47, 55, 57, 59, 61, 63, 65, 67, 69, 73, 75, 77, 79, 81, 83, 89, 91, 93, 95, 97, 99, 101, 103, 107, 109, 111, 10 113, 115, 117, 119, 121, 123, 127, 129, 131, 133, 135, 137, 138, 140, 142, 144, 146, 148, 150, 153, 155, 157, 158, 160, 162, 164, 166, 168, 172, 174, 176, 178, 180, 182, 184, 186, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 15 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, and 414. In a particularly preferred embodiment, the nucleic acid sequence is selected from the group consisting of SEQ ID NO:'s 73, 184, 186 and 242. [00020] In another embodiment, the invention provides a method for detecting a tumor cell 20 by detecting the expression of an antigen of a tumor-associated polypeptide which comprises screening tissue or cells with antibodies specific for an antigen expressed by a tumor associated polypeptide, wherein the polypeptide is selected from the group consisting of SEQ ID NO:'s 10, 12, 14,16, 20, 24, 46, 28, 30, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 25 118, 120, 124, 126, 128, 130, 132, 134, 136, 139, 141, 143, 145, 147, 149, 151, 152, 154, 156, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 231, 233, 235, 237, 239, 241, 243, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 30 363, 365, 367, 369, 371, 373, 375, 379, 381, 383, 385, 387, 389, 391, 393, 397, 399, 401, 403, 405,

407, 409, 411, 413 and 415. In a preferred embodiment, the invention provides a method for detecting an antigen expressed by a tumor-associated polypeptide selected from the group consisting of SEQ ID NO:'s 74, 185, 187, 188 and 243.

[00021] In another embodiment, the invention provides a method for regulating the growth of a tumor cell which comprises regulating the expression of a nucleic acid selected from the group consisting of SEQ ID NO:'s 9, 11, 13, 15, 17, 19, 23, 25, 27, 29, 33, 35, 37, 39, 41, 45, 47, 55, 57, 59, 61, 63, 65, 67, 69, 73, 75, 77, 79, 81, 83, 89, 91, 93, 95, 97, 99, 101, 103, 107, 109, 111, 113, 115, 117, 119, 121, 123, 127, 129, 131, 133, 135, 137, 138, 140, 142, 144, 146, 148, 150, 153, 155, 157, 158, 160, 162, 164, 166, 168, 172, 174, 176, 178, 180, 182, 184, 186, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 230, 232, 234, 236, 10 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412 and 414. In a particularly preferred embodiment, the nucleic 15 acid sequence is selected from the group consisting of SEQ ID NO:'s 73, 184, 186 and 242. [00022] In another embodiment, the invention provides a method for regulating the growth of a tumor cell which comprises regulating the expression of a polypeptide selected from the group consisting of SEQ ID NO:'s 10, 12, 14,16, 20, 24, 46, 28, 30, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 20 104, 106, 108, 110, 112, 114, 116, 118, 120, 124, 126, 128, 130, 132, 134, 136, 139, 141, 143, 145, 147, 149, 151, 152, 154, 156, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 231, 233, 235, 237, 239, 241, 243, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 25 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 379, 381, 383, 385, 387, 389, 391, 393, 397, 399, 401, 403, 405, 407, 409, 411, 413 and 415. In a preferred embodiment, the invention provides a method for detecting an antigen expressed by a tumor-associated polypeptide selected from the group consisting of SEQ ID NO:'s 74, 184, 185, 187, 188 and 243. 30

[00023] In another embodiment, the invention provides a method for vaccinating an animal to

protect the animal from developing a tumor which comprises administering to the animal an immunogen comprising a polypeptide encoded by a nucleic acid selected from the group consisting of SEQ ID NO:'s 10, 12, 14,16, 20, 24, 46, 28, 30, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 124, 126, 128, 130, 132, 134, 136, 139, 141, 143, 145, 147, 149, 151, 152, 154, 156, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 231, 233, 235, 237, 239, 241, 243, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271,

273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311,

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313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 379, 381, 383, 385, 387, 389, 391, 393, 397, 399, 401, 403, 405, 407, 409, 411, 413 and 415. In a preferred embodiment, the animal is a human and the immunogen comprises a polypeptide encoded by SEQ ID NO:'s 74, 185, 187, 188 and 243.

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DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the methods of the present invention can be used to classify data [00024] from original dbEST and UNIGENE databases in a table form (Baranova et al., FEBS Letters, 508, 143-148 (2001)). The HSAnalyst program is one type of software program that can be used to assemble the EST sequences and clusters using the methods of the present invention. This program is available at (http://pcn197.vigg.ru/programs/HSAnalyst.exe). In one preferred embodiment, the methods of the invention comprise the compiling of a supplemental database which contains only those sets of EST's that can specifically be associated with expression in either a particular abnormal (e.g., tumor)or normal physiological condition or tissue type. In one embodiment, the supplemental database includes EST entries from all human cDNA libraries that can specifically be classified as «tumor» or «normal» by tissue source. The supplemental database utilized in the demonstrative examples of the present invention contains a carefully checked description of each included library, cross-referenced from different data sources such as dbEST, UNIGENE and CGAP web-sites, which are available at the National Institutes of Health web site (www.ncbi.nlm.nih.gov), TIGR (www.tigr.org) and Stratagene (www.stratagene.com). The supplemental database thus contains a classification of all cDNA libraries as either tumor or normal.

Approximately 4000 entries in the supplemental database describing cDNA sources were classified according to their origin from tumor or normal tissues (cells). In checking the libraries, those obtained from "premalignant", "non-cancerous pathology" and "immortalized cells" were not included in the supplemental database. In other embodiments, one or more databases can be utilized in the methods of the invention without modifying in a supplemental database. In the case of the databases used in the demonstrative examples presented herein, some of the libraries were considered undefined due to lack of information or ambiguity of information.

[00025] EST pre-classification in the supplemental databases for other possible tasks not described herein can be performed by users themselves

10 [00026] HSAnalyst software was able to arrange EST data in the supplemental database according to any given parameter, e.g. tissue type or the number of ESTs contained in a cluster. As will readily be appreciated by persons of ordinary skill in the art, classification of ESTs according to tissue types requires verification of available database information on expression patterns and is the most time-consuming stage. Depending on the type of tissue being analyzed for global expression patterns, a specific database may contain and compare only sequences that are conclusively known to be expressed in a given cell type or physiological state. Classification of the data can be performed by many variations of software capable of handling large groups of data from the UniGene database without deviating from the scope of the present invention.

[00027] In one embodiment, the present invention provides a method for the detection of tumor markers wherein the CDD approach is utilized to search various publicly available databases containing human EST's. This gene-hunting procedure was inspired by the hypothesis that tumors may provide conditions for the expression of some transcribed units that are not expressed in any normal tissues. Instead of pairwise comparison of each tumor and corresponding normal tissue, a differential display of all available tumor libraries against all available normal libraries was performed.

[00028] A particular feature of the methods of the present invention includes subtracting all available clusters containing more than 10% of normal-derived ESTS from a whole set of the UniGene clusters to identify clusters associated with a particular phenotype, instead of pairwise comparisons of each tumor and corresponding normal tissue.

30 [00029] EST's present a particularly useful set of sequence data to analyze with the methods of the present invention. GenBank included 3,900,480 human ESTs as of November 16, 2001.

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These sequences and the methods of the present invention were used to generate Table 1 discussed infra. UniGene includes all human ESTs clustered by homology. It should be noted that as available sequence data on EST's continues to grow, these numbers correspondingly change. The methods of the present invention will be equally applicable, however, to the evolving database resources which continue to become available for sequence analysis.

[00030] Most EST's can be traced to a certain tissue source, including tumor and normal ones. In a particularly preferred embodiment, the comparison of tumor and normal libraries is performed on a supplemental database referred to herein as "LibraryRegistry", which comprises a supplemental database that contains only those EST's that clearly are defined as originally detected in normal or tumor tissue samples, as discussed above. It can readily be appreciated by persons of ordinary skill in the art that similar methods can be employed to "customize" a database to include only sequences known to be associated with a particular phenotype or cell type and a defined set of "normal" sources which provide sequences that can be distinguished from the cell or phenotype of interest. Just as the present invention provides tumor-associated EST's and compares these to other human EST's, an example is also provided which compares EST's reported from stress-induced Arabidopsis and EST's from Arabidopsis that are not from plants exposed to the stress conditions. [00031] A preferred embodiment of the invention utilizes a method of sequence comparison to determine tumor-associated EST's. This method is demonstrated on tumor-specific sequences but as noted is applicable to any well-described database which provides information on the origin of nucleic acid sequences contained therein. In the first step, a database of clustered EST sequences containing a description of the source for each of the sequences is selected for analysis. In the second step, for each cluster the number of its ESTs is retrieved from the cluster description. Next, the number of ESTs from the "tumor" cDNA libraries is counted. The whole range of possible EST numbers is dissected into sub ranges. The arrangement of sub ranges can be performed exponentially (e.g., sub ranges with exponents 1-2, 3-4, 5-8, 9-16) or linearly (sub ranges with factors 1-10, 11-20, 21-30). Simultaneously, the tumor ESTs/all ESTs percentage is calculated for each cluster and those clusters which exceed a user-defined bottom threshold value for the percentage of tumor ESTs/all ESTs are listed in the output file as tumor specific clusters.

[00032] The subranges can be arranged exponentially (e.g., sub ranges with exponents 1-2, 3-30 4, 5-8, 9-16) or linearly (sub ranges e.g. with factors 1-10, 11-20, 21-30). Classification of subranges into linear or logarithmic format provides two complementary ways for statistical

estimation of a threshold level for determining whether a cluster is associated with a particular phenotype. Using the methods of the present invention, arrangement of subranges produced successful detection of tumor-associated markers whether subranges were arranged linearly as in Table 1 or logarithmically. Program output is designed to separate information about each set of clusters of the same size. In general it is possible to choose some intervals within the whole range of cluster sizes (cluster "size" is the number of EST's in a cluster). For example, if one needs the detailed picture of tumor clusters distribution it may be useful to choose narrow intervals, even assigning a cluster to as little as 1 EST sequence. For each interval the following values are calculated: total number of ESTs contained in clusters of the size within the interval N_{EST} , total number of these clusters N_{clust} and the number of tumor related clusters N_{tum} within this interval. Tumor related clusters that have relative content of tumor tissue-derived ESTs over the threshold denoted as «t» given by user (usually from 90% to 100%). Also, the theoretically expected number of tumor clusters within this interval is calculated. To let a computer program do this, the user must input the expected content p of tumor-related ESTs in the whole database. Given the N_{EST} and N_{clust} for the interval it is assumed that tumor cluster distribution is binomial so the expected number of tumor clusters is $N_{tum} = N_{clust} * \sum_{m} C_{m}^{n} p^{m} (1-p)^{n-m}$ where p is mean tumor ESTs content in database (declared by user). The sum in the brackets is calculated for each m: n*t < m < n, where n varies between the interval edges and represents the hypothetical cluster size. The 90-100% threshold range described above for cell type-associated clusters in humans is for the case of human tumorassociated EST's but this number can vary depending on the difference between the expected number of clusters at a given t for a cluster size versus the observed number of clusters at a given t for the cluster size. In an exemplary analysis using the methods of the present invention, the database

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[00033] In an exemplary analysis using the methods of the present invention, the database LibraryRegistry was analyzed. This library provided a database of EST's from human normal and tumor sources. The EST's were placed in clusters based on homology; for each cluster the total number of EST's within the cluster was determined, the clusters were then ordered sequentially based on the number of EST's in each cluster and divided into subranges linearly based on the number of EST's per cluster as shown in Table 1. For each cluster subrange obtained the number EST's within said cluster expressed in tumor cells was determined. Next, based on a normal distribution, the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in tumor cells was calculated, wherein the threshold percentage was

calculated at 90% and 100%. The number of clusters in each subrange observed to contain 90% or 100% tumor-specific EST's was determined. Next, subranges having an observed number of clusters that meet said predetermined threshold percentage five times greater than the number of clusters expected to meet said predetermined threshold for the subrange according to normal distribution were noted. Clusters in the subranges between 17 and 2048 were determined to contain 5 times or greater the number of expected clusters having 90% or more tumor-derived EST's in the cluster subrange were identified. These clusters were than associated with the corresponding Hs. Identifying number from the Unigene database to determine the nucleic acid sequences which were tumor-associated sequences.

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[00034] To be sure that what was found was a "true" tumor-associated cluster not generated by chance among the total number of EST clusters classified with the methods of the present invention, the theoretical number of "tumor" clusters for every sub range is calculated. This is done utilizing an underlying model of a unimodal binomial distribution with the mean value of "tumor/all" percentage that can be defined by the user (0 to 100%). This binomial method is used to determine the expected number of tumor/all for predetermined thresholds for each cluster size based on the proportion of EST's from tumor cells in the database. In the example described in Table 1, the subranges which were analyzed for 90% or more tumor derived EST's were subranges that contained at least five times more such clusters than expected for the cluster size. This ratio of observed to expected has been found by the inventors to be reliable for determining phenotype or cell type associated clusters utilizing databases from Arabidopsis, human and mouse. It will readily be appreciated by persons of ordinary skill in the art that other ratios of observed/expected clusters for a predetermined threshold will also be useful. As little as 3.5 times the number of observed/expected clusters equal to or greater than the threshold range are also contemplated. Clusters between 3.5 and 5 times the number of expected clusters may also identify useful subranges displaying the predetermined threshold percentage of sequences for a cluster. Alternatively, an observed number of clusters for subrange that is at least one standard deviation greater than the number of clusters expected for a subrange may also be used to identify useful subranges displaying the predetermined threshold percentage of sequences for a cluster. [00035] Referring now to Table I, the expected numbers of tumor-specific clusters that exceeded threshold values were calculated for a UniGene database of human EST's that was

available on November 6, 2001. A comparison between the expected and observed tumor-derived

EST's demonstrated that tumor-related clusters were not accidental but represented a natural phenomenon. In this example, user-derived threshold values for the percentage of tumor-derived EST's to all EST's were at least 90% tumor-derived EST's per cluster and 100% tumor-derived EST's per cluster. When at least 90% of the EST's in a cluster are tumor derived, the cluster is referred to as tumor-associated. Each cluster was identified with a representative nucleic acid sequence based on the Hs. number for the sequence and the representative longest nucleotide sequence or defined mRNA sequence associated with the cluster.

[00036] Referring now to Table II, there are shown the results of tumor-related clusters detected with the methods of the present invention on a Unigene database that was assembled May 3, 2002. Except for the methods otherwise noted, the methods used to determine markers for tumors were as described for Table II. All of the tumor associated clusters in Table II had a number of EST's per cluster of 10 or more, which was found to be a significant number of EST's that would be tumor-associated using the methods described herein for identifying subranges having an observed number of clusters that was five times more than the expected number of clusters that met a predetermined threshold of 90% or more tumor derived sequences. Among the 196 tumor related clusters detected, 93 are non-coding and 103 encode at least one polypeptide sequence. Among clusters encoding a polypeptide, six correspond to known genes previously described as tumor markers/antigens, as indicated in Table 2.

[00037] Differentially expressed EST clusters are useful as markers for a physiological state or phenotype and prognostic indicators and may be suitable targets for various therapeutic interventions. Therapeutic interventions can include use of various gene therapy techniques to regulate the expression of the sequences, target-associated antibodies to inhibit growth of cells expressing phenotype associated marker polypeptides, and use of marker polypeptides as immunogens to vaccinate an animal against cells expressing the marker.

25 [00038] Useful diagnostic techniques include, but are not limited to fluorescent in situ hybridization (FISH), direct DNA sequencing, PFGE analysis, Southern blot analysis, single stranded conformation analysis (SSCA), RNase protection assay, allele-specific oligonucleotide (ASO), dot blot analysis and PCR-SSCP, as discussed in detail further below. Also useful is the recently developed technique of DNA microchip technology.

30 [00039] "Antibodies." The present invention also provides polyclonal and/or monoclonal antibodies and fragments thereof, and immunologic binding equivalents thereof, which are capable

of specifically binding to the tumor-associated polypeptides and fragments thereof or to polynucleotide sequences from the tumor-associated region, particularly from the tumor-associated locus or a portion thereof. The term "antibody" is used both to refer to a homogeneous molecular entity, or a mixture such as a serum product made up of a plurality of different molecular entities.

Antibodies to the tumor-associated markers will be useful in assays as well as pharmaceuticals.

[00040] As used herein, the term "computer" is meant to refer to at least one computer but can also include more than one computer connected by any means known in the art of computer science. Furthermore, the term is also meant to include a computer interacting with a remote computer or other server which provides access to a plurality of databases via the world wide web. In one embodiment, the analysis of EST clusters is performed on software on a computer while the

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In one embodiment, the analysis of EST clusters is performed on software on a computer, while the information imported to the computer for correlation is obtained from contact with the world wide web.

[00041] Alteration of mRNA expression for the tumor markers of the present invention can be detected by any techniques known in the art. These include Northern blot analysis, PCR amplification and RNase protection. Alteration of expression of tumor-associated genes can also be detected by screening for alteration of the expression of the protein encoded by a tumor-associated gene. For example, monoclonal antibodies immunoreactive with a marker polypeptide can be used to screen a tissue using methods known in the art. These include Western blots, immunohistochemical assays and ELISA assays. Functional assays, such as protein binding determinations, can be used and assays biochemical function of a tumor-associated marker can be employed.

[00042] Genes or gene products can also be detected in human body samples, such as serum, stool, urine and sputum and isolated tumor tissue. The same techniques discussed above for detection of genes or gene products in tissues can be applied to other body samples. Cancer cells are sloughed off from tumors and appear in such body samples. In addition, the gene product itself may be secreted into the extracellular space and found in these body samples even in the absence of cancer cells. By screening such body samples, a simple early diagnosis can be achieved for many types of cancers. In addition, the progress of chemotherapy or radiotherapy can be monitored more easily by testing such body samples for genes or gene products. The diagnostic methods of the present invention is useful for clinicians, so they can decide upon an appropriate course of treatment.

[00043] Pairs of single-stranded DNA primers can be annealed to sequences within or surrounding a tumor-associated gene in order to prime amplifying DNA synthesis of the gene itself. A complete set of these primers allows synthesis of all of the nucleotides of the gene coding sequences, i.e., the exons. The set of primers preferably allows synthesis of both intron and exon sequences. The primers themselves can be synthesized using techniques which are well known in the art. Generally, the primers can be made using oligonucleotide synthesizing machines which are commercially available. Given the sequences of the tumor associated genes of the invention, design of particular primers is well within the skill of the art.

[00044] The nucleic acid probes provided by the present invention are useful for a number of purposes. They can be used as probes to detect PCR amplification products derived from the mRNA of the gene or to detect actual mRNA transcripts directly in tumors or other cells being analyzed for expression of tumor-associated markers.

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"Probes". Polynucleotide probes form a stable hybrid with a of the target sequence, under highly stringent to moderately stringent hybridization and wash conditions. If it is expected that the probes will be perfectly complementary to the target sequence, high stringency conditions will be used. Hybridization stringency may be lessened if some mismatching is expected, for example, if variants are expected with the result that the probe will not be completely complementary. Conditions are chosen which rule out nonspecific/adventitious bindings, that is, which minimize noise. In general, hybridizations conditions will be stringent conditions.

[00046] Probes for the tumor-associated markers may be derived from the sequences of the region or its cDNAs. The probes may be of any suitable length, which span all or a portion of the marker, and which allow specific hybridization to the transcripts expressed from the marker. If the target sequence contains a sequence identical to that of the probe, the probes may be short, e.g., in the range of about 8-30 base pairs, since the hybrid will be relatively stable under even highly stringent conditions. If some degree of mismatch is expected with the probe, i.e., if it is suspected that the probe will hybridize to a variant region, a longer probe may be employed which hybridizes to the target sequence with the requisite specificity.

[00047] The probes may include an isolated polynucleotide attached to a label or reporter molecule and may be used to isolate other polynucleotide sequences, having sequence similarity by standard methods. Other similar polynucleotides may be selected by using homologous polynucleotides. Alternatively, polynucleotides encoding these or similar polypeptides may be

synthesized or selected by use of the redundancy in the genetic code. Various codon substitutions may be introduced, e.g., by silent changes (thereby producing various restriction sites) or to optimize expression for a particular system.

[00048] Probes comprising synthetic oligonucleotides or other polynucleotides of the present invention may be derived from naturally occurring or recombinant single- or double-stranded polynucleotides, or be chemically synthesized. Probes may also be labeled by nick translation, Klenow fill-in reaction, or other methods known in the art.

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[00049] Portions of the polynucleotide sequence having at least about eight nucleotides, usually at least about 15 nucleotides, and fewer than about 6 kb, usually fewer than about 1.0 kb, from a polynucleotide sequence encoding the tumor associated markers of the invention are preferred as probes. Thus, this definition includes probes of 8, 12, 15, 20, 25, 40, 60, 80, 100, 200, 300, 400 or 500 nucleotides or probes having any number of nucleotides within these ranges of values (e.g., 9, 10, 11, 16, 23, 30, 38, 50, 72, 121, etc., nucleotides), or probes having more than 500 nucleotides. The probes may also be used to determine whether mRNA encoding a tumor-associated marker is present in a cell or tissue. The present invention contemplates the use of probes having at least 8 nucleotides derived from a tumor-associated marker of the invention and any combination of these sequences as described in further detail below, its complement or functionally equivalent nucleic acid sequences.

[00050] Similar considerations and nucleotide lengths are also applicable to primers which may be used for the amplification of all or part of the tumor-associated markers of the invention. Thus, a definition for primers includes primers of 8, 12, 15, 20, 25, 40, 60, 80, 100, 200, 300, 400, 500 nucleotides, or primers having any number of nucleotides within these ranges of values (e.g., 9, 10, 11, 16, 23, 30, 38, 50, 72, 121, etc. nucleotides), or primers having more than 500 nucleotides, or any number of nucleotides between 500 and 9000. The primers may also be used to determine whether mRNA encoding a tumor-associated marker is present in a cell or tissue.

[00051] Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, or organic solvents, in addition to the base composition, length of the complementary strands, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. Stringent temperature conditions will generally include temperatures in excess of 30°C, typically in excess of 37°C, and preferably in

excess of 45°C. Stringent salt conditions will ordinarily be less than 1000 mM, typically less than 500 mM, and preferably less than 200 mM. However, the combination of parameters is much more important than the measure of any single parameter.

[00052] Probe sequences may also hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well known in the art.

Methods of Use: Nucleic Acid Diagnosis and Diagnostic Kits

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[00053] In order to detect the presence of neoplasia, the progression toward malignancy of a precursor lesion, or as a prognostic indicator, a biological sample of the lesion is prepared and analyzed for the presence or absence of the expression of a tumor-associated marker. Results of these tests and interpretive information are returned to the health care provider for communication to the tested individual. Such diagnoses may be performed by diagnostic laboratories, or, alternatively, diagnostic kits are manufactured and sold to health care providers or to private individuals for self-diagnosis.

Initially, the screening method may involve amplification of the relevant sequences. [00054] In another preferred embodiment of the invention, the screening method involves a non-PCR based strategy. Both PCR and non-PCR based screening strategies can detect target sequences with a high level of sensitivity.

[00055] The most popular method used today is target amplification. Here, the target nucleic acid sequence is amplified with polymerases. One particularly preferred method using polymerasedriven amplification is the polymerase chain reaction (PCR). The polymerase chain reaction and other polymerase-driven amplification assays can achieve over a million-fold increase in copy number through the use of polymerase-driven amplification cycles. Once amplified, the resulting nucleic acid can be sequenced or used as a substrate for DNA probes.

[00056] When the probes are used to detect the presence of the target sequences, the biological sample to be analyzed, such as blood or serum, may be treated, if desired, to extract the nucleic acids. The sample nucleic acid may be prepared in various ways to facilitate detection of the target sequence; e.g. denaturation, restriction digestion, electrophoresis or dot blotting. The targeted region of the analyte nucleic acid usually must be at least partially single-stranded to form 30 hybrids with the targeting sequence of the probe. If the sequence is naturally single-stranded, denaturation will not be required. However, if the sequence is double-stranded, the sequence will

probably need to be denatured. Denaturation can be carried out by various techniques known in the art.

[00057] Analyte nucleic acid and probe are incubated under conditions which promote stable hybrid formation of the target sequence in the probe with the putative targeted sequence in the analyte. The region of the probes which is used to bind to the analyte can be made completely complementary to a targeted region. Therefore, high stringency conditions are desirable in order to prevent false positives. However, conditions of high stringency are used only if the probes are complementary to regions of the chromosome which are unique in the genome. The stringency of hybridization is determined by a number of factors during hybridization and during the washing procedure, including temperature, ionic strength, base composition, probe length, and concentration of formamide. Under certain circumstances, the formation of higher order hybrids, such as triplexes, quadraplexes, etc., may be desired to provide the means of binding target sequences.

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[00058] Detection, if any, of the resulting hybrid is usually accomplished by the use of labeled probes. Alternatively, the probe may be unlabeled, but may be detectable by specific binding with a ligand which is labeled, either directly or indirectly. Suitable labels, and methods for labeling probes and ligands are known in the art, and include, for example, radioactive labels which may be incorporated by known methods (e.g., nick translation, random priming or kinasing), biotin, fluorescent groups, chemiluminescent groups (e.g., dioxetanes, particularly triggered dioxetanes), enzymes, antibodies and the like. Variations of this basic scheme are known in the art, and include those variations that facilitate separation of the hybrids to be detected from extraneous materials and/or that amplify the signal from the labeled moiety. A number of these variations are reviewed in e.g., U.S. Patent 4,868,105, and in EPO Publication No. 225,807.

Once a sufficient quantity of desired tumor-associated polypeptide has been obtained, it may be used for various purposes. A typical use is the production of antibodies specific for binding. These antibodies may be either polyclonal or monoclonal, and may be produced by in vitro or in vivo techniques well known in the art. For production of polyclonal antibodies, an appropriate target immune system, typically mouse or rabbit, is selected. Substantially purified antigen is presented to the immune system in a fashion determined by methods appropriate for the animal and by other parameters well known to immunologists. Typical sites for injection are in footpads, intramuscularly, intraperitoneally, or intradermally. Of course, other species may be substituted for mouse or rabbit. Polyclonal antibodies are then purified using techniques known in

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the art, adjusted for the desired specificity.

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[00060] An immunological response is usually assayed with an immunoassay. Normally, such immunoassays involve some purification of a source of antigen, for example, that produced by the same cells and in the same fashion as the antigen. A variety of immunoassay methods are well known in the art.

[00061] Monoclonal antibodies with affinities of 10-8 M-1 or preferably 10-9 to 10-10 M-1 or stronger will typically be made by standard procedures. Briefly, appropriate animals will be selected and the desired immunization protocol followed. After the appropriate period of time, the spleens of such animals are excised and individual spleen cells fused, typically, to immortalized myeloma cells under appropriate selection conditions. Thereafter, the cells are clonally separated and the supernatants of each clone tested for their production of an appropriate antibody specific for the desired region of the antigen.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides, or alternatively, to selection of libraries of antibodies in phage or similar vectors. The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent agents, chemiluminescent agents, magnetic particles and the like. Patents teaching the use of such labels include U.S. Patents 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149 and 4,366,241. Also, recombinant immunoglobulins may be produced (see U.S. Patent 4,816,567).

Methods of Use: Peptide Diagnosis and Diagnostic Kits

25 [00063] Antibodies (polyclonal or monoclonal) may be used to detect the absence or absence of peptides encoded by tumor-associated markers of the invention. Techniques for raising and purifying antibodies are well known in the art and any such techniques may be chosen to achieve the preparations claimed in this invention. In a preferred embodiment of the invention, antibodies will immunoprecipitate proteins from solution as well as react with proteins on Western or immunoblots of polyacrylamide gels. In another preferred embodiment, antibodies will detect tumor-associated proteins in paraffin or frozen tissue sections, using immunocytochemical

techniques. Antibodies specific to tumor-associated markers described herein can be employed in conjunction with toxic products that can be bound to the antibodies and selectively delivered to tumor cells via binding of the antibody with the tumor-associated polypeptide present on or in the tumor cell utilizing techniques well known in the art.

[00064] Preferred embodiments relating to methods for detecting tumor-associated proteins include enzyme linked immunosorbent assays (ELISA), radioimmunoassays (RIA), immunoradiometric assays (IRMA) and immunoenzymatic assays (IEMA), including sandwich assays using monoclonal and/or polyclonal antibodies. Exemplary sandwich assays are described by David et al. in U.S. Patent Nos. 4,376,110 and 4,486,530.

10 Methods of Use: Antisensense and siRNA Therapy

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[00065] The present invention contemplates an antisense polynucleotide up to about 50 nucleotides in length that hybridizes with mRNA molecules that encode a tumor-associated polypeptide, and the use of one or more of those polynucleotides in treating cancer cells. See U.S. Patent Nos. 5,891,858 and 5,885,970, incorporated herein by reference, for further details. The antisense polynucleotide or siRNA is useful for treating cancer caused by expression of a tumor-specific or tumor-associated polypeptide. In a similar manner, siRNA molecules specific for tumor-associated nucleic acid markers of the invention can also be used to suppress transcription of said marker sequences.

[00066] In one embodiment an antisense polynucleotide or siRNA is contacted with a cancer cell. The contact is carried out in vivo in a host animal, and contact is effected by administration to the animal of a pharmaceutical composition containing the polynucleotide dissolved or dispersed in a physiologically tolerable diluent so that a body fluid such as blood or lymph provides at least a portion of the aqueous medium. In vivo contact is maintained until the polynucleotide is eliminated from the mammal's body by a normal bodily function such as excretion in the urine or feces or enzymatic breakdown. The polynucleotide may be injected directly into the tumor in an aqueous medium (an aqueous composition) via a needle or other injecting means and the composition is injected throughout the tumor as compared to being injected in a bolus. For example, an aqueous composition containing an antisense polynucleotide or siRNA, the inverts or mixtures thereof is injected into tumors via a needle. The needle is placed in the tumors and withdrawn while expressing the aqueous composition within the tumor. That mode of administration is carried out in three approximately orthogonal planes in the tumors.

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[00067] This administration technique has the advantages of delivering the polynucleotide directly to the site of action and avoids most of the usual body mechanisms for clearing drugs. Tumors can be located using e.g., modern imaging techniques such as X-ray, ultrasound and MRI so that exact placement of the polynucleotide can be carried out.

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[00068] A polynucleotide can also be administered in the form of liposomes. As is shown in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain stabilizers, preservatives, excipients, and the like in addition to the agent.

[00069] An antisense polynucleotide or siRNA can also be administered by gene therapy. The polynucleotide may be introduced into the cell in a vector such that the polynucleotide remains extrachromosomal. In such a situation, the polynucleotide will be expressed by the cell from the extrachromosomal location. Vectors for introduction of polynucleotides for extrachromosomal maintenance are known in the art, and any suitable vector may be used. Methods for introducing DNA into cells such as electroporation, calcium phosphate coprecipitation and viral transduction are known in the art, and the choice of method is within the competence of a person of ordinary skill in the art.

[00070] The antisense polynucleotide or siRNA, may be employed in gene therapy methods in order to decrease the amount of the expression products in cancer cells, especially in those cases where overexpressed. Such gene therapy is particularly appropriate for use in both cancerous and pre-cancerous cells.

[00071] Gene therapy would be carried out according to generally accepted methods, for example, as described in further detail in U.S. Patent No. 5,747,282 and references cited therein, all incorporated by reference herein. Expression vectors in the context of gene therapy are meant to include those constructs containing sequences sufficient to express a polynucleotide that has been cloned therein. In viral expression vectors, the construct contains viral sequences sufficient to support packaging of the construct. If the polynucleotide encodes an antisense polynucleotide or siRNA or ribozyme, expression will produce the antisense polynucleotide or siRNA or ribozyme. Thus in this context, expression does not require that a protein product be synthesized. In addition to the polynucleotide cloned into the expression vector, the vector also contains a promoter

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functional in eukaryotic cells. The cloned polynucleotide sequence is under control of this promoter. Suitable eukaryotic promoters include those described above. The expression vector may also include sequences, such as selectable markers and other sequences conventionally used.

[00072] Gene transfer techniques which target DNA directly to specific tumor cell types are preferred. Receptor-mediated gene transfer, for example, is accomplished by the conjugation of DNA (usually in the form of covalently closed supercoiled plasmid) to a protein ligand via polylysine. Ligands are chosen on the basis of the presence of the corresponding ligand receptors on the cell surface of the target cell/tissue type. These ligand-DNA conjugates can be injected directly into the blood if desired and are directed to the target tissue where receptor binding and internalization of the DNA-protein complex occurs. To overcome the problem of intracellular destruction of DNA, coinfection with adenovirus can be included to disrupt endosome function. Methods of Use: Transformed Hosts; Transgenic/Knockout Animals and Models

In one embodiment of the invention, a transgene is introduced into a non-human host [00073] to produce a transgenic animal expressing a human or murine tumor-specific or tumor-associated gene. The transgenic animal is produced by the integration of the transgene into the genome in a manner that permits the expression of the transgene. Methods for producing transgenic animals are generally described e.g., in U.S. Patent No. 4,873,191.

Transgenic animals may be produced from the fertilized eggs from a number of [00074] animals including, but not limited to reptiles, amphibians, birds, mammals, and fish. Within a particularly preferred embodiment, transgenic mice are generated which overexpress the polypeptide. Alternatively, the absence of the polypeptide in «knock-out» mice permits the study of the effects that loss of protein has on a cell in vivo. Knock-out mice also provide a model for the development of cancers.

[00075] Methods for producing knockout animals have been described previously. The production of conditional knockout animals, in which the gene is active until knocked out at the desired time is also known by those of ordinary skill in the art.

[00076] As noted above, transgenic animals and cell lines derived from such animals may find use in certain testing experiments. In this regard, transgenic animals and cell lines capable of expressing a tumor-specific or tumor-associated gene may be exposed to test substances. These test substances can be screened for the ability to reduce overexpression of the gene or impair the expression or function of a protein encoded by the gene.

[00077] In another embodiment, the invention provides a method for assaying expression of EST's utilizing microarrays comprising antibodies to the tumor-associated EST's of the invention.

[00078] In another embodiment, the invention provides a method for assaying for tumor EST's utilizing microarrays containing polypeptides or fragments thereof encoded and expressed by the tumor-associated EST's of the invention.

[00079] In another embodiment, the invention provides a method for assaying for tumor-associated EST's utilizing microarrays comprising nucleic acids specific for the tumor-related EST's of the invention.

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[00080] The newly developed technique of nucleic acid analysis via microchip technology is also applicable to the present invention. In this technique, literally thousands of distinct oligonucleotide probes are built up in an array on a silicon chip. Nucleic acid to be analyzed is fluorescently labeled and hybridized to the probes on the chip. It is also possible to study nucleic acid-protein interactions using these nucleic acid microchips. Using this technique one can determine the presence of a sequence or expression levels of a gene of interest. The method is one of parallel processing of many, even thousands, of probes at once and can tremendously increase the rate of analysis.

[00081] It is also known in to persons of ordinary skill in the art that microchip technology is applicable to screening large numbers of samples by detecting antibody/antigen interactions. Utilizing cell type specific transcripts detected with the methods of the present invention, large numbers of cells from different stages of expression can be screened for expression of antigens. For a general description, see e.g., U.S. patent No. 6,379,895.

[00082] The nucleic acid, protein or antibody to the protein encoded by the nucleic acid may also be incorporated on a microarray. The preparation and use of microarrays are well known in the art. Generally, the microarray may contain the entire nucleic acid or protein, or it may contain one or more fragments of the nucleic acid or protein. Similarly, the microarray may contain an antibody or only the portion of the antibody necessary for binding antigen. It is contemplated by the invention that single chain antibodies may be utilized in the detection of tumor antigen or portions thereof. Suitable nucleic acid fragments may include at least 17 nucleotides, at least 21 nucleotides, at least 30 nucleotides or at least 50 nucleotides of the nucleic acid sequence, particularly where the nucleic acid marker comprises a coding sequence. Suitable protein fragments may include at least 4

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amino acids, at least 8 amino acids, at least 12 amino acids, at least 15 amino acids, at least 17 amino acids or at least 20 amino acids.

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[00083] In another embodiment, the invention provides methods for vaccinating an animal with tumor-associated polypeptides of the invention as an immunogen. A method of vaccination can comprise administering at least a fragment of a polypeptide encoded by the tumor-associated markers of the present invention. Methods for the administration of such fragments of a peptide are known to a person of ordinary skill in the art and can include administering additional peptide sequences as an adjuvant. In a preferred embodiment, the peptides are administered under conditions which will elicit a cytotoxic T-cell response to a tumor expressing a tumor-associated marker described in the present invention.

Cytotoxic T Lymphocytes (CTL) are an important means by which a mammalian organism defends itself against cancer. Functional studies of viral and tumor-associated T cells have confirmed that a minimal cytotoxic epitope consisting of a peptide of 8-12 amino acids can prime an antigen presenting cell to be lysed by CD8⁺ CTL, as long as the antigen presenting cell presents the epitope in the context of the correct MHC molecule. It is contemplated that the immunogen may comprise a minimal cytotoxic epitope on the tumor marker polypeptide. Minimal cytotoxic epitopes generally have been most effective when administered in the form of a lipidated peptide together with a helper CD4 epitope. Peptides administered alone, however, also can be highly effective.

[00085] As used herein, the singular form "a", "an", "said" and "the" include plural references unless the context clearly indicates otherwise. For example, a reference to a "cell" would include a plurality of cells.

[00086] As used herein, the terms "diagnosing" or "prognosing," as used in the context of neoplasia, are used to indicate 1) the classification of lesions as neoplasia, 2) the determination of the severity of the neoplasia, or 3) the monitoring of the disease progression, prior to, during and after treatment.

"Encode". A polynucleotide is said to "encode" a polypeptide if, in its native state or when manipulated by methods well known to those skilled in the art, it can be transcribed and/or translated to produce the mRNA for and/or the polypeptide or a fragment thereof. The anti-sense strand is the complement of such a nucleic acid, and the encoding sequence can be deduced therefrom.

[00088] "Isolated" or "substantially pure". An "isolated" or "substantially pure" nucleic acid (e.g., an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.

[00089] As used herein, the terms "tumor-associated marker" and "stress-associated marker" are meant to include nucleic acids or fragments thereof and polypeptides or fragments thereof that are specifically disclosed herein as associated with the indicated phenotype, as well as other nucleic acids or polypeptides or fragments thereof that comprise said polypeptides and nucleic acids and fragments thereof that can be detected with the methods of the present invention and are not known in the prior art to be associated with the particular phenotype.

[00090] As used herein, phenotype associated "marker expression" is meant to include the expression of all or a fragment of a specific (e.g., tumor-specific) or associated (e.g., tumor-associated) marker. Thus, as will be recognized by those of ordinary skill in the art, detection of marker expression is meant to include all known methods for detecting of gene expression, including but not limited to e.g., detecting the expression of an mRNA or fragment thereof (e.g., an EST) for the marker or detecting the expression of a polypeptide or fragment thereof encoded by a tumor associated marker of the invention. Polypeptide or fragments thereof can be detected by antibodies which specifically bind to the polypeptide or fragment thereof and allow its detection in various assay as known in the art such as Western blots, ELISA and the like.

[00091] The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, immunology, cell biology, cell culture and transgenic biology, which are within the skill of the art.

General Methods

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[00092] MTC panels. We used CLONTECH Multiple Tissue cDNA (MTCTM) panels, which contain sets of normalized first-strand cDNA generated using CLONTECH Premium RNATM from different human tumors and normal tissues. These tissue-specific first strand cDNA's were used as

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templates in conjunction with tissue-specific tumor EST-derived primers in PCR studies to determine if tumor-associated EST's detected with the methods of the present invention were The following panels were used: Human Tumor MTC Panel (K1422-1), Human MTC Panel I (K1420-1), Human MTC Panel II (K1421-1), Human Immune System MTC Panel (K1426-1), and Human Fetal MTC Panel (K1425-1).

PCR analysis. PCR of genomic DNA was carried out in 25µl of the following f000931 reaction mixture: 67mM Tris-HCI (pH 8.9), 4mM MgCl₂, 16mM (NH₄)SO₄, 10mM 2mercaptoethanol, 0.1 mg/ml BSA, 200 μM (each) dNTP, specific forward and reverse primers (10 pmol each), 2.5U Taq polymerase, and 500 ng of genomic DNA. The samples were incubated in a PTC-200 thermocycler (MJ Research, USA) for the total of 35 cycles. Each cycle consisted of 30 s at 95°C, 30 s at 56°C for forv/rev16 or at 58°C for forw/rev8, forw/rev19, and forw/rev28, and 1 min at 72°C. DNA primers for PCR sequencing and the size of fragments generated for each cluster sequence were as follows:

Hs.154173:

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forward16: (SEO ID NO:1) 5'-TCT TTC TTG ATG AAT TAT CTT ATG-3';reverse16: (SEQ ID 15 NO:2) 5'-ACA CAC CCT CAT TCC CGC-3'; fragment size: 443 bp. Hs. 133294:

forward8: (SEQ ID NO:3) 5'-GTC AAC CTT CTC ATC TTC CTC-3'; reverse8: (SEQ ID NO:4) 5'-CAG GAA GTT GGG TAGATG TG-3'; fragment size: 1) 412 bp fragment size: 2) 1084 bp.

Hs. 67624: 20

> forward19:(SEO ID NO:5) 5'-TAA TTG CAT TCT TCA AAA TTC TAC-3'; reverse19: (SEQ ID NO:6) 5'-GCT TCG CAC CAT TGAATA AAC-3'; fragment size: 315 bp. Hs.133107:

forward 28: (SEQ ID NO:7) 5'-TAC ATA GTT GTT ATC TTA AGG TG-3';

25 reverse 28: (SEQ ID NO:8) 5'-TGG GAA TTC TAT ACT TTT GAC-3'; fragment size: 344 bp. [00094] The expression of nucleotide sequences under study was analyzed in different tissues using CLONTECH cDNA panels and Titanium Taq PCR kit (K1915-I). Reaction mixtures of a 25ul volume were prepared according to the manufacturer's instructions for cDNA panels. PCR was carried out under the following conditions: 1 min at 95°C, 35 cycles consisting of 30 s at 95°C, 30 s at 56°C, for forw/rev16 or at 58°C, for forw/rev8, forw/rev19, or forw/rev28, and 1 min at 68°C. 30 The terminal stage of the reaction was 5 min at 68°C.

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[00095] Electrophoresis. The amplification products were separated by electrophoresis in 2% agarose gel and detected by staining with ethidium bromide. 8µl of PCR mixture was taken per lane.

- [00096] Computer programs. Homology searches were performed using BLAST computer programs on a NCBI server (www.ncbi.nlm.nih.gov). Exon-intron boundaries and putative gene elements were predicted using program tools using techniques well known in the art and described in detail for example at the WebGene server (http://www.itba.mi.cnr.itlwebgene/) and on the search engine of Baylor College of Medicine. (http://kiwi.imgen.bcm.tmc.edu:8088/search-launcher/launcher.html).
- 10 Determination of exon-intron boundaries are indicative of genes as transcribed genomic units producing pre-mRNA spliced during RNA maturation.

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[00097] The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known by persons of ordinary skill in the art and/or the techniques specifically described herein were utilized.

EXAMPLE 1

[00098] Utilizing publicly available EST sequence data and HSAnalyst, available clusters were organized into the ranges shown in Table 1. The software utilized in this example made possible the arrangement of sub ranges exponentially (e.g., sub ranges with exponents 1-2, 3-4, 5-8, 9-16) or linearly (sub ranges with factors 1-10, 11-20, 21-30). In this Example, the sub ranges were arranged linearly. Totally, 2681 libraries were classified as "tumor" libraries, while 1087 libraries were classified as "normal". The supplemental database resulting from this differential comparison contained 921,237 "tumor" ESTs and 810,097 "normal" ESTs. Of these, 83 EST clusters were identified as putative tumor markers, possessing a percentage of tumor-specific EST's/total EST's of at least 90%. The classes of tumor related EST clusters revealed by the methods of the present invention were further classified into five distinct categories based on information provided about the sequences in the public databases, as detailed below in Tables 3-6. The clusters found to be tumor related included non-coding mRNAs, non-coding mRNAs with strict tumor specific expression, genes that encode proteins with weak homology to known proteins (as used herein, "weak refers to statistically significant homology that is not indicative of function or inclusion in

the same gene family), genes that encode known proteins and genes that encode known proteins with a tumor associated expression. In some instances, EST clusters are tumor specific, not being expressed in the normal EST libraries. In other instances, the tumor EST's detected are tumor related, i.e., expressed at significantly higher levels in tumor cells versus normal cell sources. Table 1 represents an analysis of the number of tumor-associated EST's observed with the methods of the present invention.

Table I

Sub-range of # of EST's per cluster	EST numbe	r	Tumor specific EST's, %	Number of tur	nor-specific clust	ers at threshold,	% *
	# EST's per sub-range	# clusters per sub-range		>	90%	1	00%
				Observed	Expected	Observed	Expected
1-2	59111	44373	42%	18342	23073	18342	23073
3-4	45400	13401	35%	1880	1884	1880	1884
5-8	53569	8742	37%	567	279	567	172
9-16	63421	5407	39%	168	5	99	4
17-32	83968	3607	41%	45	0	17	0
33-64	176845	3762	43%	16	0	2	0
65-128	349008	3790	45%	10	0	2	0
129-256	460493	2588	47%	8	0	0	0
257-512	339482	975	50%	3	0	0	0
513-1024	208171	303	53%	1	0	0	0
1025-2048	130524	96	57%	0	0	0	0
2049-4096	95180	36	60%	0	0	0	0
4097-8192	49804	10	66%	0	0	0	0
8193-16384	14725	1	67%	0	0	0	0

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[00099] An exemplary method for detecting tumor-associated EST's comprised retrieving sequence data on EST's from all available EST's, arranging the EST's into individual clusters based on homology, identifying EST's expressed in tumor cells and, for each cluster, calculating the percentage of the number of ESTs expressed in tumor cells to all EST's contained in the cluster. A threshold value for the percentage of the number of ESTs expressed in tumor cells to all ESTs for each cluster was chosen to identify tumor related clusters. In one example, the percentage of tumorderived EST's to normal EST's per cluster was a user-defined threshold of at least 90%. Clusters having a percentage of EST's expressed in tumor cells to all EST's for a cluster greater than the threshold value were considered as tumor-associated. Thus, tumor-associated markers represent those nucleic acid or polypeptide or fragments thereof that comprise at least 90% of the sequences in an EST cluster. Some sequences observed were markers that represented nucleic acid or polypeptides or fragments thereof that comprised 100 % of the sequences in a cluster. [000100] In Table I, there are shown the results of detection of clusters observed at different ranges, with the number of observed tumor related clusters observed versus the number calculated or expected. Clusters were sorted into ranges on a linear basis in this example. [000101] Using global analysis of cluster data with the methods of the present invention, it has

been demonstrated that the sequences of Table 2 represent tumor-associated sequences.

	ID NO:	SEQ. ID NO: 12	SEQ. ID NO: 14		SEQ. ID NO: 18	ID NO:	SEQ. ID NO: 22	SEQ. ID NO: 24	SEQ. ID NO: 26	ION GI	SEQ. ID NO: 30	SEQ. ID NO: 32	SEQ. ID NO: 34	SEQ. ID NO: 36
REFERENCE NUCLEOTIDE SEQUENCE	SEQ. ID NO: 9	SEQ. ID NO: 11	SEQ. ID NO: 13	SEQ. ID NO: 15	SEQ. ID NO: 17	SEQ. ID NO: 19	SEQ. ID NO: 21	SEQ. ID NO: 23	SEQ. ID NO: 25	ID NO:	SEQ. ID NO: 29	SEQ. ID NO: 31		SEQ. ID NO: 35
SURFACE, IF KNOWN KNOWN TUMOR MARKER INDICATED	SURFACE				SURFACE, KNOWN TUMOR MARKER	KNOWN MARKER FOR LEUKEMIA	KNOWN TUMOR MARKER	SURFACE	RARANEOPLASTIC MARKER	SURFACE	KNOWN MARKER FOR GLIOMA	KNOWN MARKER FOR GERM CELL TUMORS	SURFACE	
TUMOR TYPES	Choriocarcinoma, glioma, germ cell tumors, lung carcinoma, teratocarcinoma	small cell lung carcinoma, pancreatic carcinoma, intestinal carcinoma, ovary carcinoma	12	Pancreatic carcinoma, glioma, cervical carcinoma, lung carcinoma, uterine carcinoma, germ cell tumors, gastric carcinoma, colon carcinoma, salivary gland carcinoma, bladder carcinoma	stomach carcinoma, colon carcinoma	Glioma, retinoblastoma, lung carcinoid tumors, pancreatic insulinoma	1.4	lung carcinoid tumors, lung carcinomas	lung carcinomas, pancreatic carcinoma	Rhabdomyosarcoma	Rhabdomyosarcoma, germ cell tumors, leiomyosarcoma, ovarian tumors, melanoma, burkitt lymphoma	gastric carcinoma, germ cell tumors, uterus carcinoma, ovarian tumors, reratocarcinoma, lung tumor	melanoma, glioma, rhabdomyosarcoma neuroblastoma, colon carcinoma, lymphoma	cervical carcinoma , leiomyosarcoma, rhabdomyosarcoma glioma , teratocarcinoma, neuroblastoma , prostate
UNIGENE GENE NAME	CCKBR (Cholecystoki-nin B rcceptor)	DLX2 (Distal-less homeo box 2	APOBEC1 ApolipoproteinB mRNA editing enzyme, cata-lytic polypeptide 1	ALDH3Al (Aldehydedehydrogenase 3 family, member Al)	GUCY2C Guanylate cyclase 2C (heat stable enterotoxin receptor)	LMO1 LIM domain only 1 (rhombotin	ASCL1 Achaete-scute complex-like 1 (Drosophila-like)	KCNN4 Potassium voltage-gated channel, shaker-related subfamily, member 4	DSG3 Desmoglein 3 (pemphigus vulgaris antiden)	CHRNAl Cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle)	GLI Glioma-associated oncogene homolog (zinc finger protein)	POUSFI POU domain, class 5, transcription factor 1	SLC7Al Solute carrier family 7 (cationic amino acid transporter, y+system), member 1	ZNF74 Zinc finger protein 74 (Cos52)
UNIGENE	Hs.203	Hs.419	нз.560	Нз.575	Hs. 1085	Hs.1149	Hs.1619	Hs.1854	нз.1925	нв.2266	Нs.2693	H8.2860	нs.2928	Нв.3057

TABLEII

carcinoma, colon carcinoma, colon carcinoma, colon carcinoma, bladder transitional		prostate carcinoma, bladger carcinoma, kidney hypernephroma, ovarian tumors, lung carcinoma	or Colon carcinoma, kidney tumors, germ cell SEQ. ID NO: 39 SEQ. ID NO: tumors, stomach carcinoma	Pancreatic carcinoma, colon carcinoma, bladder transitional cell papilloma, ovarian carcinoma, breast carcinoma, lung carcinoma			family 12 Lymphoma, colon, ovarian, stomach, SURFACE SEQ. ID NO: 47 SEQ. ID NO: prostate, endometrial and hepatic carcinomas	parathyroid tumor KNOWN TUMOR MARKER SEQ. ID NO: 49 SEQ. ID NO:	intestine duodenal carcinoma, glioma, pharynx squamous cell, uterus, ovarian, FOR MELANOWA melanoma	Lung carcinoma, bladder transitional cell KNOWN TUMOR MARKER SEQ. ID NO: 53 SEQ. ID NO: papilloma, T cell leukemia, genitourinary FOR MELANOWA tract transitional cell tumors	lung carcinoma SURFACE SEQ. ID NO: 55 SEQ. ID NO:	glioma, prostate carcinoma, uterus SURFACE SEQ. ID NO: 57 SEQ. ID NO: 57 SEQ. ID NO: 59 SQ. ID NO: 50 SEQ. ID NO: 50 SQ. ID NO:	
Car	KIAA0042 (KIAA0042 gene product) Lei		EPS8R3 Epidermal growth factor Col receptor pathway substrate 8 tum related brotein 3	703 gene product)	PRAME Preferentially expressed Bra antigen in melanoma car car car car car car car car car ca	LOC55924 Hypothetical protein Ret	e carrier family 12 loride member 8	one	MAGEA4 Melanoma antigen, family int A,4	MAGEA9 Melanoma antigen, familyA, 9 Lur par tre	SCGB2A2 Secretoglobin, family 2A, lur member 2	ip junction protein, beta 6	ESTS, Weakly similar to
	Hs.3104		Hs. 5366	Нв.6168	нs.30743	Hs.30751	нв.36793	Hs.37045	Нв.37107	Hs.37110	Hs.46452	Hs.48956	Hs.49605

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SEQ. 1D NO: 62	ID NO:	ID NO:	SEQ. ID NO: 68	ID NO:	SEQ. ID NO: 72 SEQ. ID NO: 72	ID NO:	SEQ. ID NO: 76		SEQ. ID NO: 80	SEQ. ID NO: 82	SEQ. ID NO: 84		SEQ. ID NO: 86		SEQ. ID NO: 8		SEQ. ID NO: 5	ID NO:	ID NO:	SEQ. ID NO: 9
ž	S	S	σ.	SO G	es es	S	S	·	S	S	S		Ω		S	ω	S	8	2	S
SEQ. ID NO: 61	SEQ. ID NO: 63	ID NO:	SEQ. ID NO: 67	SEQ. ID NO: 69		SEQ. ID NO: 73	SEQ. ID NO: 75	SEQ. ID NO: 77	SEQ. ID NO: 79	SEQ. ID NO: 81	SEO, ID NO: 83		SEQ. ID NO: 85		SEQ. ID NO: 87	SEQ. ID NO: 89	SEQ. ID NO: 91	SEQ. ID NO: 93	ID NO:	SEQ. ID NO: 97
							SURFACE	SURFACE	SECRETED		KNOWN MARKER-	BREAST CARCINOMA POSSIBLYPROSTATIC CARCINOMA)	Embryonal	carcinoma stem cell-associated marker; Possibly GERM CELL TUMORS	KNOWN TUMOR MARKER		SURFACE			
melanoma, choriocarcinoma, B-cell chronic lymphotic leukemia, germ cell, uterus serous carcinoma, stomach carcinoma, retinoblastoma, sarcoma,	Kidney tumors, germ cell tumors, colon carcinoma	letomyosarcoma	Endometrial, pancreatic, lymphoma, lung	melanoma, teratocarcinoma, germ cell	tumors, stomach carcinoma, hypernephroma,	Germ Cell tumors	B-cell chronic lymphocytic leukemia,	arcinoma,	Nervous tumors, colon carcinoma,	Lymphoma, uterus carcinoma, kidney Carcinoma, lung carcinoid tumors, ovarian	Description colon andometrial, breast.	lung, ovarian, stomach, prostate carcinomas and giloma	germ cell tumors, neuroepithelial tumors		choriocarcinoma, breast carcinoma, endometrium carcinoma, melanoma, stomach carcinoma	ovarian tumors	neuroblastoma, lung carcinoma, small intestine carcinoma	Pancreas, endometrial, ovarian carcinomas, lung carcinoid tumors and germ cell tumors	ovarian tumors	Ovarian carcinoma, retinoblastoma, endometrium carcinoma
COL9A3 Collagen, type IX, alpha 3	HNF4A Hepatocyte nuclear factor	pax1 paired box dene 1	POMS	HOXA1 Homeobox A1		SMOa	Membrane-bound phosphatidic acid-	DRD2 Dopamine receptor D2	PRHZ Proline-rich protein HaeIII	FABPGratty acid binding protein	The state of the s	First transcription factor	GDF3 Growth differentia-tion	factor 3	CTAG2 Cancer/testis antigen 2	7MO9	CHRWA3 Cholinergic receptor,	POMB similar to S29539 ribosomal protein 113a, cytosolic	POM9	KIAA1484 KIAA1484 protein
нз.53563	Hs.54424	He 54567	Hs. 66357	Hs. 67397		100 6762A	HB. 68864	Нв.73893	Нв.73952	Нв.74126	* 1000	F	HR 86232		нs.87225	Hs.89143	Hs.89605	нв.97258	Ня.97283	Hs.97860

нз. 98988	POM10 Homo sapiens, clone IMAGE:4425111, mRNA, partial cds	germ cell tumors, hypernephroma, ovarian tumors, colon, uterus, stomach, pancreas, skin squamous cell carcinomas		SEQ. ID NO: 99	SEQ. ID NO: 100
нв.99624	POM11	parathyroid tumor, ovarian tumor, Stomach carcinoma		SEQ. ID NO: 101	SEQ. ID NO: 102
нв.99960	MS4A3 Membrane-spanning 4- domains, subfamily A, member 3 (hematopoieticcell-specific)	Lung carcinoma, chronic myelogenous leukemia, prostate carcinoma	SURFACE	SEQ. ID NO: 103	SEQ. ID NO: 104
Hs.103504	ESR2 Estrogen receptor 2 (ER beta)	germ cell tumors, lung carcinoma, neuroblastoma	KNOWN TUMOR MARKER	SEQ. ID NO: 105	SEQ. ID NO: 106
Hs.103707	MUCSAC Mucin 5, subtypes A and C, tracheobron-chial/gastric	COLON, PANCREATIC, STOMACH CARCINOMAS, LUNG TUMORS	SURFACE, MARKER FOR COLON AND GASTRIC CARCINOMAS	SEQ. ID NO: 107	SEQ. ID NO: 108
нв.104073	POM12	Colon, stomach carcinoma		SEQ. ID NO: 109	SEQ. ID NO: 110
Hs.104115	ZNF10 Zinc finger protein 10 (KOX1)	parathyroid, lung carcinoid, nervous cell tumors, adrenal cortex carcinoma, germ cell tumors, uterus tumor, multiple myeloma		SEQ. ID NO: 111	SEQ. ID NO: 112
Hs.105484	REG-IV Regenerating gene type IV	Prostate, duodenal, colon and stomach carcinomas, B-cell chronic lymphocytic leukemia, acute myelogenous leukemia		SEQ. ID NO: 113	SEQ. ID NO: 114
Hs.105667	POM13	ovarian tumors		SEQ. ID NO: 115	ID NO:
Hs.105924	DEFB4 Defensin, beta 4	Head and neck carcinoma	SECRETED	SEQ. ID NO: 117	SEQ. ID NO: 118
нв.112341	PI3 Protease inhibitor 3, skinderived (SKALP)	Glioma, B-cell chronic lymphocytic leukemia, uterus, lung and colon carcinomas, ovarian, prostate, colon carcinomas, bladder, nervous cell and placenta tumors		ID NO:	ID NO:
Hs.113262	HTR45 hydroxytryptamine (serotonin) receptor 4	Schwannoma	SURFACE	SEQ. ID NO: 121 SEQ. ID NO: 123	SEQ. ID NO: 1 SEQ. ID NO: 1
Hs.114905	ERN2 (ER to nucleus signalling 2)	Stomach, colon, pancreatic carcinoma		SEQ. ID NO: 125	SEQ. ID NO: 1
Hs.117938	COL17Al Collagen, type XVII, alpha l	glioma, pancreas, lung, colon, nasopharyngeal, stomach carcinomas, germ cell, bladder, uterus tumors,		SEQ. ID NO: 127	SEQ. ID NO: 1
Hs.122310	POM14	parathyroid tumor		SEQ. ID NO: 129	SEQ. ID NO: 1
Hs.123094	SALL1 Sal-11ke 1 (Drosophila)	Retinoblastoma, germ cell tumors, glioma		SEQ. ID NO: 131	SEQ. ID NO: 1
нв.123993	POM15 Weakly similar to T00366 hypothetical protein KIAA0669	Glioma, colon carcinoma, lung carcinoid tumors , parathyroid tumor		SEQ. ID NO: 133	SEQ. ID NO: 1
Hs.124173	POM16	parathyroid tumor		SEQ. ID NO: 135	SEQ. ID NO: 1
Hs.124638	POM17	COLON CARCINOMA		SEQ. ID NO: 137	

нв.125293	POM18	Glioma, lung carcinoma, kidney tumors, germ cell tumors, parathyroid tumor, stomach carcinoma, ovary		SEQ. ID NO: 138	SEQ. ID NO: 139
нз.126566	POM19	Carcinoma Colon carcinoma		SEO. ID NO: 140	SEO. ID NO: 141
Hs.126869	POM20	LUNG CARCINOID TUMORS, germ cell tumor		ID NO:	ID NO:
HB.127144	POM21			SEQ. ID NO: 144	SEQ. ID NO: 145
нв.127383	POM22	Colon carcinoma		SEQ. ID NO: 146	ID NO:
Hs.127476	POM23	Lung carcinoid tumors, glioma, kidney		SEQ. ID NO: 148	SEQ. ID NO: 149
	AIGHLY SIMLIAT TO BIGZ HUMAN BIGZ PROTEIN PRECURSOR	tumors, cnongrosarcoma, germ cell tumors, Ewing's sarcoma			
нs.128001	POM24	COLON CARCINOMA		SEQ. ID NO: 150	SEQ. ID NO: 151 SEQ. ID NO: 152
нs.128115	PON25 Homo sapiens cDNA FLJ32217 fls, clone PLACE6003771	germ cell, lung carcinoid and kidney tumors, glioma, melanoma		SEQ. ID NO: 153	ID NO:
нз.128326	POM26	口		SEQ. ID NO: 155	SEQ. ID NO: 156
нз.128398	POM27	Lung carcinoid tumors		SEQ. ID NO: 157	
Нв.128436	POM28, Moderately similar to	Lung carcinoid tumors		SEQ. ID NO: 158	SEQ. ID NO: 159
	putative secreted protein [Homo sapiens]				
нв.128437	POM29, Weakly similar to 833477 hypothetical protein 1 - rat	Lung carcinold tumors, kidney tumors, cervical carcinoma		SEQ. ID NO: 160	SEQ. ID NO: 161
Нв.128907	POM30, Weakly similar to	LUNG CARCINOID TUMORS		SEQ. ID NO: 162	SEQ. ID NO: 163
	orthopedia homolog (Drosophila); orthopedia (Drosophila) homolog:				
	orthopedia (Drosophila) homolog;				
	Orthopedia, homolog of Drosophila qene [Homo sapiens] [H.sapiens		;		
Hs.129040		parathyroid tumor, lung carcinoid tumors		SEQ. ID NO: 164	SEQ. ID NO: 1
нв.129108	POM32	Lung carcinoid tumors		SEQ. ID NO: 166	SEQ. ID NO: 1
	clone IMAGE:2337282			-	
нв.129302	POM33	lung carcinoma, germ cell tumors		SEQ. ID NO: 168	SEQ. ID NO: 1
нэ.129782	MUC3B Mucin 3B	Pancreatic carcinoma, kidney tumors, colon carcinoma choriocarcinoma, breast carcinoma, stomach tumor, head and neck	PROBABLY KNOWN TUMOR MARKER	SEQ. ID NO: 170	SEQ. ID NO: 1
HR 131358	POM34	cumor, lung tumor, ovary tumor		SEO. ID NO: 172	SEQ. ID NO: 1
Нв.132370	NOX1 NADPH oxidase 1	colon carcinomas, glioma, lung carcinoid			SEQ. ID NO: 1
13257 BH	Datrad how gone o	Ting Carcinoma parathornid timor.		ID NO:	
	ratter nov deile o	stonach carcinoma, head and neck			
		Carcinoma			

Hs.133081	POM35 Homo sapiens cDNA FLJ25124 fis	Esophagus carcinoma, germ cell tumors, glíoma, lung carcinoma, chondrosarcoma, uterus carcinoma	SEQ. ID NO: 180	SEQ. ID NO: 181
нs.133089	DFFB DNA fragmentation factor, 40 kD, beta polypeptide (caspase- activated DNase)	Lung carcinoid tumors, breast carcinoma, colon carcinoma, nervous cell tumor, leiomioma, acute myelogenous leukemia, osteosarcoma	SEQ. ID NO: 182	SEQ. ID NO: 183
нв.133107	POM36	Ovary carcinoma, lung carcinoma, glioma	SEQ. ID NO: 184	SEQ. ID NO: 185
нs.133294	POM37	Uterus carcinoma, lung carcinoma, Ovary carcinoma, chronic myelogenous leukemia, breast carcinoma, glioma, colon juvenile granulosa tumor, adrenal adenoma, prostate tumor, haden and neck carcinoma	SEQ. ID NO: 186	SEQ. ID NO: 187 SEQ. ID NO: 188
Hs.133296	РОМЗВ	Ovary carcinoma, lung carcinoma	SEQ. ID NO: 189	SEQ. ID NO: 190
нв.133300	POM39	Breast carcinoma, ovary carcinoma, lung carcinoma	ID NO:	
Hs.133451	POM40	germ cell tumors, colon carcinoma	SEQ. ID NO: 193	SEQ. ID NO: 194
нз.135365	POM41	Pancreatic carcinoma, ovarian carcinoma,	SEQ. ID NO: 195	SEQ. ID NO: 196
Hs.140457	POM42	Kidney tumors, lung carcinoid tumorss, insulinoma, glioma, cervical carcinoma, stomach tumors	SEQ. ID NO: 197	SEQ. ID NO: 198
нв.142907	POM43 Human BRCA2 region, mRNA sequence CG011	Lung carcinoid tumors, fibrotheoma, ovary tumors, uterus tumors	SEQ. ID NO: 199	SEQ. ID NO: 200
Hs.143507	T T, brachyury homolog	<pre>Lung carcinoma, B-cell chronic lymphocytic lackemia, breast carcinoma, carm cell timora</pre>	SEQ. ID NO: 201	SEQ. ID NO: 202
Hs.143949	POM44	Colon carcinoma	SEQ. ID NO: 203	SEQ. ID NO: 2
Hs.144063	POM45	Lung carcinoid tumorss	SEQ. ID NO: 205	SEQ. ID NO: 2
Hs.144121	POM46, Moderately similar to hypothetical protein, MNCb-123; hypothetical protein, MNCb-1231	glioma, lung carcinoma	SEQ. ID NO: 207	SEQ. ID NO: 2
Нв.145327	POM47	chronic myelogenous leukemia, Ovary carcinoma, colon carcinoma, lung carcinoma, head and neck carcinoma	SEQ. ID NO: 209	SEQ. ID NO: 2
Hs.145340	POM4B	lung carcinoma, Ovary carcinoma, head and neck carcinoma	SEQ. ID NO: 211	SEQ. ID NO: 2
Hs.145356	POM49	Ovary carcinoma, lung carcinoma	SEQ. ID NO: 213	SEQ. ID NO: 2
Hs.145357	L	Ovary carcinoma, breast carcinoma, head and neck carcinoma, lung carcinoma	SEQ. ID NO: 215	SEQ. ID NO: 2
Hs.145489	POM51	Ovary carcinoma	SEQ. ID NO: 217	SEQ. ID NO: 2

Hs.145492	POM52	Ovary carcinoma, lung carcinoma		SEQ. ID NO: 219	SEQ. ID NO: 220
Hs.145493	POM53			ID NO:	ID NO:
Н9.145500	POM54	Ovary carcinoma, lung carcinoma		ID NO:	ID NO:
Нв.145509	POMSS	լսա		SEQ. ID NO: 225	SEQ. ID NO: 226
Hs.145661	POMS6	,		SEQ. ID NO: 227	SEQ. ID NO: 228
Нз.145809	POM57, Weakly similar to T31613 hypothetical protein Y50E8A.i -	Uterus carcinoma, stomach carcinoma, pancreatic carcinoma, placenta tumor		SEQ. ID NO: 229	
	Caenorhabditis elegans				
Нв.146200	POMSB	Ovary carcinoma, breast carcinoma, head and neck carcinoma		ID NO:	ID GI
Hs.147291	POM59	germ cell tumors			ID NO:
Hs.148661	РОМ60	Lung carcinoid tumors, germ cell tumors		SEQ. ID NO: 234	SEQ. ID NO: 235
нв.152290	POMG1, Highly similar to VIPS HUMAN VASOACTIVE INTESTINAL POLYEPETIDE RECEPTOR 2 PRECURSOR [H. saniens]	Rhabdomyosarcoma, gliona, colon carcinoma		SEQ. ID NO: 236	SEQ. ID NO: 237
Нв.152531	HANDI Heart and neural crest	Neuroblastoma, Schwannoma, germ cell tumors, sarcoma		SEQ. ID NO: 238	SEQ. ID NO: 239
He 153444		Lung carcinoid tumors, breast carcinoma		SEQ. ID NO: 240	SEQ. ID NO: 241
нв.352562	POMG3, Home sapiens cDNA FLJ33010 fls, clone THYWU1000336 Unidens aluster identifier He 154173 has been retired			SEQ. ID NO: 242	SEQ. ID NO: 243
	current cluster Hs. 352562	colon carcinoma, breast carcinoma, melanoma, skin carcinoma, prostate tumor			
Hs.155981	MSLN Mesothelin	Pancreas, prostate, cervical, liver, uterus, colon, stomach, head and neck and lung carcinomas, choriocarcinoma, glioma, ovarian and uterus tumors, chondrosarcoma	KNOWN TUMOR MARKER FOR SOME CARCINOMAS		
Hs.156213	POM64	Lung carcinoid tumors, head and neck carcinoma, colon carcinoma			SEQ. ID NO: 2
Hs.156499	POM65	Uterus tumors, Lymhomas and leukemias		SEQ. ID NO: 248	SEQ. ID NO: 2
нз.156637	CBLC Cas-Br-M (murine) ectropic retroviral transforming sequence c	stomach, lung, breast, colon, lung pancreas and head and neck carcinomas, glioma, choritocarcinoma Uterus and carcinoid tumors		SEQ. ID NO: 250	SEQ. ID NO: 2
HR 146762	POM66	derm cell tumors		ID NO:	SEQ. ID NO: 2
нs.156810	POM67 Weakly similar to EF11 HUMAN ELONGATION FACTOR 1- ALPHA 1 (H. Sapiens)	Úterus carcinoma			
Hs.156813	POM68 (MGC10600) predicted protein MGC10600	Melanoma, choriocarcinoma, germ cell tumor		SEQ. ID NO: 256	SEQ. ID NO: 2

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Hs.156843 POM69	POM69	Lung carcinoid tumors, germ cell tumors,	SEQ. ID NO: 258	SEQ. ID NO: 259
		melanoma		
Hs.156905	KIAA1676	germ cell and lung carcinoid tumors,	SEQ. ID NO: 260	SEQ. ID NO: 261
		Ewing's sarcoma, ovary, adrenal cortex		
_		and uterus carcinomas, retinoblastoma		
Hs.157205	Hs.157205 BCAT1 Branched chain	germ cell tumors, lung carcinoma, glioma,	SEQ. ID NO: 262	SEQ. ID NO: 263
	aminotransfe-rase 1, cytosolic	lymphoma, teratocarcinoma,		
		rhabdomyosarcoma, lung carcinoma,		
		embryonal carcinoma, uterus tumor		
Hs. 79707	TNFRSF191 Tumor necrosis factor	Colon carcinoma, glioma, B-cell chronic	SEQ. ID NO: 264	SEQ. ID NO: 265
	receptor superfamily, member 19-	lymphocytic leukemia, ovary tumors, germ		
	llike	cell tumors, chondrosarcoma,		
=		neuroblastoma, melanoma, stomach		
	UniGone cluster identifier	carcinoma , leiomyosarcoma, renal cell		_
	He.158218 has been retired now	carcinoma, uterus carcinoma, lung		
	Hs. 79707	carcinoma, lymphoma, pre-B cell acute		
		lymphoblastic leukemia		
Нв.158333	PRSS7 Protease, serine, 7	Glioma, breast carcinoma	SEQ. ID NO: 266	SEQ. ID NO: 267
	(enterokinase)			
Hs.158460	Hs.158460 CDK5R2 Cyclin-dependent kinase 5,	germ cell tumors, lung carcinoid tumors,	SEQ. ID NO: 268	SEQ. ID NO: 269
-	regulatory subunit 2 (p39)	glioma, adrenal cortex carcinoma, lung		
		carcinoma, neuroblastoma		
нз.158521	POM70	Kidney tumors, breast carcinoma	SEQ. ID NO: 270	SEQ. ID NO: 271
ня.160724	POM71	glioma, lung carcinoid tumors	SEQ. ID NO: 272	SEQ. ID NO: 273
Hs.162717	POM72,	Choriocarcinoma, neuroblastoma, placenta	SEQ. ID NO: 274	SEQ. ID NO: 275
	(MGC15668) Hypothetical protein	tumor, lung, colon, stomach carcinomas		
	MGC15668	germ cell tumors, burkitt lymphoma,		

SEQ. ID NO: 277			SEQ. ID NO: 281	SEQ. ID NO: 283	SEQ. ID NO: 285	SEQ. ID NO: 2	ID NO:	SEQ. ID NO: 2	SEQ. ID NO: 2	:ON GI			SEQ. ID NO: 3	SEQ. ID NO: 3	SEQ. ID NO: 3
SEQ. ID NO: 276			SEQ. ID NO: 280	SEQ. ID NO: 282	SEQ. ID NO: 284	SEQ. ID NO: 286		SEQ. ID NO: 290	1		ID NO:		ID NO:	ĽΩ NO:	SEQ. ID NO: 304
Melanoma, rhabdomyosarcoma, renal cell carcinoma, mucoepidermoid carcinoma, uterus carcinoma, B-cell chronic lymphotic leukemia, colon carcinoma, lymphotic leukemia, colon carcinoma, lymphoma, ovary fibrotheoma, lung carcinoma, kidney tumors, breast carcinoma, glioma, parathyroid tumor, tumor, lung carcinoid tumors, liposarcoma, small intestine duodenal carcinoma, genitourinary tract translitonal cell tumors, head and neck carcinoma, melanoma, endometrium carcinoma, adrenal cortex carcinoma, osteosarcoma, oral carcinoma, synovial	sarcoma, lung carcilluma, lenal cell carcilnoma, chondrosarcoma, breast carcilnoma, melanoma, melingioma, lymphoma, chronic myelogenous leukemia, embryonal cell carcilnoma	Lung carcinoid tumors, lung carcinoma	Colon carcinoma	Ovary carcinoma	Ovary tumors, glioma, lung carcinoma, breast colon and pancreatic carcinoma, kidney tumors, leiomyosarcoma, uterus tumors	Ridney tumors, prostatic carcinoma	retinoblastoma, melanoma, letinoblastoma, melanoma, letomyosarcoma, Wilms tumor, breas rhabdomyosarcoma, acute myelogenous leukemla, burkitt	Lymphoma Sycotete Cercinome	טונסגריים ביינים איניים איניי	Ovary carcinoma Skin carcinoma, breast carcinoma, lung	Inno carcinoma, breast carcinoma	Luna carcinoid tumors, kidney tumors	ovarian carcinoma, kidney tumors	Prostate, stomach and bladder carcinoma	lung carcinoid tumors, germ cell tumors, breast carcinoma
TPARL TPA regulated locus		PON73, Moderately similar to POLZ HUMAN RETROVINUS-RELATED POL POLYPROPERN (H. ARDIEDS)	EVX1 Eve, even-skipped homeo box		NYLS Myosin, light polypeptide 5, regulatory	30000	POM/5 POM/6 (MGC2705) predicted MGC2705	Z 1, 100 g	╅	CLSP Calmodulin-like skin protein	BOK19	DOMBO	20000	POM91	POM92
нs.236510		нв.356072	Нв.336963	HR 170046	Н8.170482	50000	Hs.172330		Hs.172603	HB.330485 HB.180142	100001	18.320001	182362	He 185831	HB.189358

Hs.190488	POM93 (Homo sapiens mRNA; cDNA DKFZp667M2411 (from clone DKFZp667M2411)	Skin squamous cell carcinoma, stomach carcinoma, colon carcinoma, parathyroid turnor, lung carcinoma, parathyroid turnor, lung carcinoma, lymphoma, melanoma, uterus carcinoma, prostate carcinoma, carcinoma, retinoblastoma, carrical carcinoma, renal carcinoma, renal carcinoma, carcinoma, investagenous leukemia, hypernephroma, uterus carcinoma, leiomioma	SEQ. ID NO: 306	SEQ. 1D NO: 30/
Hs.191574	POM94 (Homo sapiens cDNA FLJ13050 fis, clone NT2RP3001432)	Pancreas carcinoma, parathyroid tumor, ovary tumors, teratocarcinoma, acute myelogenous leukemia, lung carcinoid tumors, hypernephroma, head and neck	SEQ. ID NO: 308	SEQ. ID NO: 309
нs.193677	ZNF141 Zinc finger protein 141 (clone pHZ-44)	Retinoblastoma, lung carcinoid tumors, hypernephroma, glioma, head and neck carcinoma ovary timors. leionioma	SEQ. ID NO: 310	SEQ. ID NO: 311
Hs.195081	POM95	germ cell tumors	SEQ. ID NO: 312	SEQ. ID NO: 313
нв.195374	POM96	<pre>germ cell tumors, B-cell chronic lymphotic leukemia, kidney tumor, uterus tumors</pre>	SEQ. ID NO: 314	ID NO:
Hs.195641	POM97	Uterus carcinoma, Iung carcinoma, colon carcinoma, nervous cell tumors, breast carcinoma, stomach carcinoma	SEQ. ID NO: 316	
Hs.196073	POM98	L	SEQ. ID NO: 318	SEQ. ID NO: 3
Ha.199460	DPCR1 DPCR1 protein	Pancreas carcinoma, stomach carcinoma	SEQ. ID NO: 320	SEQ. ID NO: 3
Hs.202247		lung carcinoid tumors	ID NO:	ID NO:
Hs.202512	<u> </u>	lung carcinoid tumors, colon carcinoma	SEQ. ID NO: 324	SEQ. ID NO: 3
Нв.202577		Schwannoma, lung carcinoid tumors, germ cell tumors, lymphoma, colon carcinoma, glioma	SEQ. ID NO: 326	ID NO:
Ha 202612	POM102	Lung carcinoma, colon carcinoma	SEQ. ID NO: 328	SEQ. ID NO: 3
на.209560	POM103	1.	SEQ. ID NO: 330	ID NO:
нв.209646	POMIO4 (KIRA1118) KIRA1118 protein	Lung carcinoma, choriocarcinoma, melanoma, glioblastoma, neuroblastoma, osteosarcoma, colon carcinoma, breast carcinoma, lymphoma, glioma,	SEQ. ID NO: 332	SEQ. ID NO: 3
Hs.211238	IL-1H1 Interleukin-1 homolog 1	retinopiastoma colon carcinoma, head and neck carcinoma	SEQ. ID NO: 334	SEQ. ID NO: 3

SEQ. ID NO: 337	SEQ. ID NO: 339					SEQ. ID NO: 341				SEQ. ID NO: 343		SEQ. ID NO: 345			SEQ. ID NO: 347	CEO TD NO. 249			SEQ. ID NO: 351		SEQ. ID NO: 353			SEQ. ID NO: 355		1.	ID NO: 3	D NO: 3			İ	SEQ. ID NO: 3		
SEQ. I	SEQ. I		_	_		SEO. I				SEQ. I		SEQ. I			SEQ. I	1 000			SEC. I		SEO. I		_	SEO. I			SEQ. I	SEQ. ID NO:				SEO. I		
SEQ. ID NO: 336	SEQ. ID NO: 338					SEQ. ID NO: 340				SEQ. ID NO: 342		SEQ. ID NO: 344			SEQ. ID NO: 346	CEO TD NO. 240	SEC. ID NO: 340		SEQ. ID NO: 350		SEQ. ID NO: 352			SEQ. ID NO: 354		- 1	SEQ. ID NO: 356	SEQ. ID NO: 358				SEQ. ID NO: 360		
					_	KNOWN TUMOR MARKER													SURFACE															
Ovary carcinoma	glioma, colon carcinoma, kidney tumors,	prostate tumors, lung	carcinoma, hypernephroma, head and neck	carcinoma, duodenal carcinoma, melanoma,	pancreatic carcinoma, uterus tumors	Pancreas carcinoma, colon carcinoma,	stomach carcinoma, head and neck	carcinoma, lung carcinoma leiomioma,	breast carcinoma	Stomach carcinoma, head and neck	carcinoma, breast carcinoma	Melanoma, ovary tumors, colon carcinoma,	parathyroid tumor, kidney tumors, head and	neck carcinoma	parathyroid_tumor		Lymphoma, germ cell tumors, nead and neck	carcinoma	B-cell chronic lymphocytic leukemia,	colon carcinoma, pancreas and carcinoma	Pancreatic carcinoma, duodenal carcinoma,	ovary carcinoma, melanoma, osteosarcoma,	glioma, leiomyosarcoma, germ cell tumors	ORAL carcionoma, cervical carcinoma, head	and neck carcinoma		Pancreas carcinoma	Hypernephroma, pancreatic carcinoma,	glioma, lung carcinoma, neuroblastoma,	renal cell carcinoma, adrenal gland	tumors	parathyroid tumor, lung carcinoid tumors,	umors, h	carcinoma, stomach carcinoma, breast
POM105	POM106		-			CEACAM5 Carcinoembryonic antigen-	related cell adhesion molecule 5			POM107 Homo sapiens cDNA FLJ11572	fis, clone HEMBA1003373	POM108			GCMB Glial cells missing homolog	ח (הדסמהוידים)	POMIUS		GPR35 G protein-coupled receptor	35	CRSP7 Cofactor required for Spl	transcriptional activation,	subunit 7 (70kD)	SERPINB13 Serine (or cysteine)	proteinase inhibitor, clade B	(ovalbumin), member 13	POM110	SLC2A6 Solute carrier family 2	(facilitated glucose	transporter), member 6	4	POM111		
HB.217766						Hs.220529		_		HB.222056		Hs.225083			Hs.227098		Hs.239107		Hs.239891		HS.241381	_		Hs.241407			Hs.243920	+-				Hs.246781		

нs.247817	H2B/S Histone family member A	Breast carcinoma, chronic myelogenous leukemia, cervical carcinoma, melanoma, ovary carcinoma, lung carcinoma, osteosarcoma, nuncepsidermoid carcinoma, duodenal carcinoma, leiomyosarcoma,	SEQ. ID NO: 362	SEQ. ID NO: 363
		glioma, prostate carcinoma, kidney tumors, colon carcinoma, prostatic intraepithelial neoplasia, lymphoma,		
		uterus carcinoma, parathyroid tumor, insulinoma, chondrosarcoma, ovary tumors, multiple myeloma, chondrosarcoma,		
		bladder tumors, parathyroid tumors, insulinoma, breast carcinoma, pnet		
нз.250158	POM112	tangray, the description of the	SEQ. ID NO: 364	SEQ. ID NO: 365
Hs.250848	Poml13Homo sapiens cDNA FLJ14761 fis. clone NT2RP3003302	Uterus carcinoma, prostate tumor, glioma, duodenal carcinoma, colon carcinoma,	SEQ. ID NO: 366	SEQ. ID NO: 367
		glioma, stomach carcinoma, Germ cell tumors, lung carcinoma, embryonal cell carcinoma, breast carcinoma,		
нз.252351	HHLA2 HERV-H LTR-associating 2	chloriacetzinoma Colon carcinoma kidney tumors, ovary tumors, Stomach tumors, prostate	SEQ. ID NO: 368	SEQ. ID NO: 369
He 253298	POM114	carcinoma, Head and neck carcinoma, germ cell tumors	SEQ. ID NO: 370	SEQ. ID NO: 371
Ha. 254379	POMILS	Ovary carcinoma	SEQ. ID NO: 372	SEQ. ID NO: 373
Us 255877	3 L MOG	Jenkemia	SEQ. ID NO: 374	SEQ. ID NO: 3
Hs.266390	POM117	Lung carcinoid tumors, pre-B cell acute Lymphoblastic leukemia, ovarian carcinoma	SEQ. ID NO: 376	SEQ. ID NO: 3
Hs.268171	POM118	Nervous cell tumors, germ cell tumors, prostatic intraepithelial neoplasia, ovary tumors	SEQ. ID NO: 378	SEQ. ID NO: 3

SEQ. ID NO: 383	3 ()	SEQ. ID NO: 3
SEQ. ID NO: 382 SEQ. ID NO: 382	SEQ. ID NO: 384 SEQ. ID NO: 386 SEQ. ID NO: 388	SEQ. ID NO: 390
Bladder carcinoma, colon carcinoma, lymphoma, prostate carcinoma, pancreas carcinoma, breast carcinoma, minas tumor, uterus carcinoma, mendingioma, kidney tumors, lung carcinoma, stomach carcinoma, parethyroid tumor, germ cell tumors, overy tumors, B-cell chronic lymphocytic leukemia, germ cell tumors, thyroid tumor, leiomyosarcoma, duodenal carcinoma, pancreatic carcinoma, alveolar thabdomyosarcoma, gloma, head and neck carcinoma, bladder transitional cell papilioma, retinoblastoma, pancreatic carcinoma, alveolar chabdomyosarcoma, Stomach carcinoma, pre-B cell acute lymphoblastic leukemia, lung carcinoma, tibrosarcoma, lymphoma, chondrosarcoma, osteosarcoma, lymphoma, chondrosarcoma, osteosarcoma, burkitt lymphoma, uterus carcinoma	Pancreas carcinoma, glioma, breast carcinoma, lung carcinoid tumors, Ewing's sarcoma, colon carcinoma, malanoma, lung carcinoma, head and neck carcinomar, carcinoma, pnet tumor Rhabdomyosarcoma, colon carcinoma, head nad neck carcinoma, epidydimal tumors, nervous cell tumors epidydimal tumors, malanoma, colon carcinoma, hepatocellular carcinoid tumors, colon carcinoma, lung carcinoma, gibrosarcoma, stomach tumor, breast carcinoma,	Stomach carcinoma
STX12 Syntaxin 12 and MGC14797 Hypothetical protein MGC14797	Pomil9, Weakly similar to B34087 Predicted protein [H.sapiens] GP6 Glycoprotein VI (platelet) DHRS2 Dehydrogenase/reductase (SDR family) member 2	POM120
106823	Hs.355428 Hs.272216 Hs.272499	Hs.273625

Нв.278291	┝╌┤	endometrial carcinoma	SEQ. ID NO: 392	SEQ. ID NO: 393
Hs.279805	POM122	<pre>Lung carcinoid tumors, nervous cell tumors, pnet tumor,</pre>	SEQ. ID NO: 394	
Hs.280146	POM123 Weakly similar to L1 repeat, Tf subfamily, member 18 [Mus musculus]	Lung carcinoid and ovarian tumors, glioma	SEQ. ID NO: 395	
ns. 109274	Pom124 NGC4365 Predicted protein MGC4365	Lung carcinoma, stomach carcinoma, colon carcinoma, breast carcinoma, gloma, kidney tumors, melanoma, choriocarcinoma, t- cell leukemia, cervical carcinoma, neuroblastoma, retinoblastoma, multiple myeloma, overy carcinoma, pre-B cell acute lymphoblastic leukemia, uterus carcinoma, kidney tumors, lung carcinoma, endometrial carcinoma, renal cell carcinoma, acute myelogenous leukemia carcinoma, acute myelogenous leukemia	SEQ. ID NO: 396	SEQ. ID NO: 397
Hs.282050	POM125 Homo sapiens CDNA FLJ31265 fis, clone KIDNE2006030, moderately similar to Gallus gallus syndesmos mRNA	Prostate carcinoma, embryonal cell carcinoma, vary earcinoma, Midney tumors, colon carcinoma, Midney tumors, colon carcinoma, germ cell tumors, neuroblastoma, retinoblastoma, melanoma, breast carcinoma, ovary tumors, renal cell carcinoma, endometrium carcinoma, letomyosarcoma, glioma, head and neck carcinoma, nervous cell tumors, neuroblastoma, cervical carcinoma, letomaria, ovarian carcinoma, head and neck tumors,	SEQ. ID NO: 398	SEQ. ID NO: 399
Hs.284203	MYOD1 Myogenic factor 3	Rhabdomyosarcoma, burkitt lymphoma	SEQ. ID NO: 400	SEQ. ID NO: 4
Нз.285026	_	Colon carcinoma	SEQ. ID NO: 402	SEQ. ID NO: 4
Нэ.285887	POM126 Weakly similar to 2109260A B cell growth factor [H.sapiens]	hepatocellular carcinoma	SEQ. ID NO: 404	
Нв.285894	POM127	hepatocellular carcinoma	SEQ. ID NO: 406	SEQ. ID NO: 4
Hs.288568	POM128 FLJ22644 Predicted protein FLJ22644	Stomach carcinoma	SEQ. ID NO: 408	SEQ. ID NO: 4

SEQ. ID NO: 411	SEQ. ID NO: 413	SEQ. ID NO: 4
SEQ. ID NO: 410	SEQ. ID NO: 412	SEQ. ID NO: 414
Lymphoma, kidney renal cell carcinoma, lung small cell carcinoma, pancreas carcinoma, choriocarcinoma, melanoma, retinolastoma, ladomyosarcoma, prostate carcinoma, head and neck carcinoma, parathyroid tumor, choriocarcinoma	ovarian carcinoma, glioma, hepatocellular	neck carcinoma, insulinoma, retinoblastoma Retinoblastoma, lelomyosarcoma, lymphoma, neuroblastoma, glioma, cervical carcinoma, pancreas carcinoma, germ cell tumors, stomach carcinoma, glioma, uterus carcinoma, lung carcinoma, glioma, uterus carcinoma, lung carcinoma, melanoma, lymphoblastic leukemia, colon cancer, endometrial carcinoma, neuroblastoma, breast carcinoma, head and neck neck carcinoma, nervous cell tumors, lung carcinoma, Wilms' tumor, pancreas
OPA3 Optic atrophy 3 (autosomal recessive, with chorea and spastic paraplegia)	POM129	TCBAP0758 Predicted protein TCBAP0758
Hs. 288842	нs.290308	на. 293678

[000102] Of the tumor associated EST's detected by the methods of the present invention, a particularly interesting group are the clusters represented by EST's found exclusively in tumor derived libraries. One striking feature of these tumor markers is their frequent occurrence in colon, lung and ovarian carcinomas. Thus, the high percentage of tumor-specific EST's is characteristic of highly malignant tumors (e.g. ovary carcinomas, metastatic breast carcinomas and small cell lung tumors. Accordingly, the methods of the present invention provide a method for predicting malignancy of a tumor based on the percentage of tumor-specific EST expression detected in such tumors. Utilizing standard molecular biology techniques as exemplified below, for example, persons of ordinary skill in the art can utilize probes for tumor associated EST's to determine the level of malignancy in a tumor tissue sample.

[000103] All three colon-specific clusters detected with the methods of the present invention represented known genes which encode apolipoprotein B mRNA editing protein APOBEC1, guanylate cyclase 2C and G protein coupled receptor 35. Both APOBEC1 and guanylate cyclase 2C mRNAs have been shown to be overexpressed in colon carcinomas (Lee et al, Gastroenterology 115(5):1096-1103 (1998); Carithers et al. Proc.Natl. Acad. Sci. USA 93(25):14827-32 (1996). Moreover, high level expression of APOBEC1 in transgenic mice and rabbit livers causes liver dysplasia and hepatocellular carcinomas and guanylate cyclase 2C appears to be relatively specific marker for the presence of metastatic colonic carcinoma cells. These observations, together with the appearance of the guanylate cyclase 2C in tumor specific clusters, indicate that this gene is a putative marker of progression of colon cancer.

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EXAMPLE 2

[000104] In order to detect the presence of a tumor associated EST in actual tissue samples, biological samples were prepared and analyzed for the presence or absence of the EST sequence. In each case, where clusters are defined by a plurality of sequences, the probes utilized are derived from the longest reported sequence for the cluster. Individual subsets of EST clusters predicted to be tumor associated with the methods of the present invention were analyzed in polymerase chain reaction studies on Clontech multiple tissues cDNA (MTC) panels and on panels of genomic DNA from different animal species. Gene or gene fragments corresponding to EST clusters Hs.133107,

Hs. 154173 and Hs. 67624 according to our computational differential display studies were expressed only in tumors. Hs. 133244 was expressed in a variety of tumors and was also expressed at very low levels in normal testis and germinal B-cells. Initially, the screening method involved a non-PCR based strategy. Such screening methods include two-step label amplification methodologies that are well known by persons of ordinary skill in the art. Both PCR and non-PCR based screening strategies can also detect target sequences with a high level of sensitivity. [000105] A subset of EST clusters found by HSAnalyst software was analyzed by both confirmatory PCR on Clontech Multiple Tissue cDNA Panels. PCR Amplification of the tumor associated EST Hs.133294 Fragment was analyzed in Human Tumor MTC Panel 1 and 2, Human 10 Immune System MTC Panel, Human Fetal MTC Panel, DNA from Different Animal species, and Southern hybridization of Hs.133294 fragment with genomic DNA from different animal species digested to completion with EcoR I. Hs.133294 represents an EST protein-encoding mRNA located on chromosome 1q21. It is weakly similar in homology to IQGA (human RAS GTPase-activatinglike protein IQGAP1). Hs.133294 was represented in: prostate tumor, HNSCC, breast carcinoma, 15 oligodendroglioma, colon carcinoma, CML, lung carcinoma, ovarian carcinoma, uterus carcinoma, adrenal adenoma and «minor occurrences» in normal testis and germinal B-cells. One EST in the cluster was derived from normal testis, one from germinal B-cells and twenty-five from different tumors. Both testis and germinal B-cells as tissues are known to express tumor markers, e.g. cancer-testis antigen family members are expressed only in testis in a healthy organism, but testis expression does not interfere with the tumor marker features of such a genes. Unlike in the case of 20 the other examples contained herein, where primers were selected from the same exon, in this case primers belong to two different exons separated by intron 672bp in size. That is why two fragments may be considered as specific to Hs.133294: a 1084 bp fragment which corresponds to unspliced mRNA and a 412 bp fragment corresponding to spliced mRNA. PCR on human tumor MTC panel produced the 1084 bp fragment on cDNAs from all eight tumors comprising the panel. The 412 bp 25 fragment was not generated in samples from prostatic adenocarcinoma, lung carcinoma and colon adenocarcinoma propagated as xenografts in athymic nude mice. The 412 bp fragment was generated in lung carcinoma and colon adenocarcinoma which have been taken as surgical explants from metastasis and primary tumor. PCR of cDNA from testis generated the 412 bp fragment detected in normal human MTC panels 1 and 2 and weak detection of the 1084 bp fragment. No

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fragments were produced on human immune system MTC panel. But on human fetal MTC panel both 1084 bp and 412 bp fragments were amplified in cDNAs from all organs and/or tissues represented in the panel. One thousand eighty four base pairs fragment corresponding to unspliced mRNA was detected in all lanes in relatively greater amounts than the 412 bp fragment. The weakest signals for both fragments were detected for fetal brain and heart.

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EXAMPLE 3

[000106] Utilizing similar methods as in Example 2, Hs.154173, a non-coding mRNA with tumor expression located in the intergenic spacer region within the rRNA encoding unit and is represented in lung carcinoma and testicular teratocarcinoma was analyzed for expression in the various tissue panels as in Example 2. PCR testing with Hs. 154173 specific primers on human tumor MTC panel resulted in amplification of an Hs.154173-specific fragment of 443 bp in the lanes corresponding to breast carcinoma and pancreatic adenocarcinoma. There was also a weak band in the lane that corresponded to prostatic adenocarcinoma.

[000107] In contrast, PCR analysis with the same Hs.154173-specific primers on normal human MTC panels 1 and 2, on human immune system MTC panel and human fetal MTC panel demonstrated no amplification of the corresponding fragment in any of 31 normal tissues cDNA comprising these four normal panels, indicating that this fragment is not expressed in these tissues.

20 EXAMPLE 4

[000108] Hs.67624 is a tumor-associated non coding mRNA located on Chromosome 3 and represented in germ cell tumors and head and neck squamous cell carcinoma. The results of PCR amplification of the tumor associated EST Hs.67624 fragment in Human Tumor MTC Panel 1 and 2, Human Immune System MTC Panel, Human Fetal MTC Panel, DNA from different animal species, and Southern hybridization of Hs.67624 fragment with genomic DNA from different animal species on genomic DNA digested to completion with EcoRI. These results confirmed that HS 67624 as a tumor associated EST expressed in ovarian carcinoma. There are three human tissues that often express tumor antigens. These are thymus, testis and embryonic tissues. PCR with Hs. 67624-specific primers on human tumor MTC panel resulted in predicted amplification of 315 bp

Hs. 67624-specific fragment in ovarian carcinoma. PCR with the same Hs.67624 primers on normal human MTC panels 1 and 2 resulted in no fragments on any of 16 normal cDNA libraries comprising these panels. PCR on human immune system MTC panel and human fetal MTC panel produced signals corresponding to 315 bp fragment only on cDNA from thymus. The signal in fetal thymus was considerably stronger than for normal thymus.

EXAMPLE 5

[000109] Hs.133107 is a tumor associated non-coding mRNA located on chromosome 12p13. The results of PCR Amplification of the EST Hs.133107 fragment in Human Tumor MTC Panel 1 and 2, Human Immune System MTC Panel, Human Fetal MTC Panel. These results confirmed that Hs. 133107 as a tumor related EST. PCR on normal Human MTC Panels 1 and 2 produced no fragments on any of cDNA from 16 normal tissues. PCR on human immune system MTC panel resulted in amplification of 344 bp fragment on cDNA from lymph node. PCR on human fetal MTC panel did not result in any fragments.

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EXAMPLE 6

[000110] The results of PCR Amplification of the a nucleic acid specific for Glucose 3 phosphate dehydrogenase fragment in Human Tumor MTC Panel 1 and 2, Human Immune System MTC Panel, Human Fetal MTC Panel and DNA from different animal species was performed as in the above examples. This control demonstrated that mRNA specific for Glucose 3 phosphate dehydrogenase could be detected in a manner consistent with known expression patterns of this gene.

EXAMPLE 7

25 [000111] The methods of the present invention were used to detect differential expression of genes expressed in hyperosmotic stress (caused by NaCl), or dehydration in the plant Arabidopsis thaliana. Despite the relatively small number of ESTs and UNIGENE clusters available for this organism, 5 stress-associated clusters were detected using the methods of the present invention. Three stress-associated clusters detected in A. thaliana represented known plant genes involved in

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stress response: GST30, Lti30 and cor15-encoding gene. The remaining clusters represented unknown genes. The applicability of the methods of the present invention to A. thaliana provides a prognostic model useful to determine if the relevant genes found in A.thaliana can be used as a hybridization templates to find orthologs in other agricultural plants and such orthologs will be useful for gene targeting etc in such important plants.

[000112] Utilizing the methods of the present invention, a database "AT Lib Registry" was constructed. This database contained descriptions of all cDNA expression libraries used to build an EST database for A. thaliana. Computer-based methods were used to determine mRNA sequences differentially expressed in plants under different physiological conditions including oxidative, herbicidal and other stress types. The CDD permitted an analysis of the absolute number of nucleotide sequences synthesized for transcription matrices of every type of interest in discovered samples. The CDD analysis utilized data from databases such as dbEST containing more than 110 000 EST sequences that were deduced from cDNA libraries made from A. thaliana cells. For every sequence in the database there was a description of source cDNA library provided. These data and the EST clustering information complete the dataset needed to describe a tissue-associated (or condition-associated) expression of transcripts of every type (or genes). The processing of large volumes of EST information was facilitated by means of a variation of the Hs. Analyst software utilized for determination of tumor-associated markers wherein the variation utilized the Hs. Analyst main module and an Arabidopsis LibRegistry, dividing the Arabodopsis libraries according to stress/non-stress categories.

[000113] The software At_Analyst was utilized to analyze EST clustering data of the model plant Arabidopsis thaliana and to conduct a comparative analysis of gene expression spectra in different tissues of the plant. In this example, all data sources were divided into 3 classes named "target1", "target2" and "undefined", whereas the last class pooled data were not entered in either of first two classes.

[000114] At Analyst software description. In this example, the source data for the program were arranged in two plain text files designated "at.data" and "libraries". The file "at.data" contained cluster descriptions arranged according to individual clusters. All fields were listed each in a separate line for each EST. Each cluster description with a field "ID" which contained the

internal UniGene cluster index, the cluster gene "title" and gene name if there was significant known homology of a cluster to a known gene, the number of sequences of any type (mRNA, protein, cDNA) included in cluster and lines containing information about all individual sequences of the cluster. For each sequence there was provided a LID (Library ID) which data field was LID used to retrieve information about the EST source library, thereby allowing association of the EST sequence with a particular physiological state or growth condition.

[000115] The database "At Library Registry" was created. This database included all source cDNA clone library descriptions of 71 libraries prepared from different parts or tissues of A. thaliana. Every record consisted of the following fields: 1) library ID in dbEST database; 2) library name; 3) tissue source of mRNA used to prepare cDNA sequences and additional comments concerning library construction methods and physiological conditions of plant growth; 4) organism name (A. thaliana in the present example); 5) organism strain or ecotype; and 6) cloning vector used for library construction. In general, source tissues were derived from A. thaliana strains Columbia Col-0, Columbia C24, Columbia GH50, Columbia gl1, Landsberg erecta and Ohio State. Some of the libraries in the database were obtained from plant parts like aboveground organs, roots, flower buds, green siliques, immature siliques, inflorescence, rosettes, seedling hypocotyls and some from different specific cell types. There were also included a number of clone libraries made from cultured cell lines of A.thaliana.

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[000116] All clone libraries in the At Library Registry were separated into four general types:

1) "untreated" indicated clone libraries made from normal plants and its parts cultivated under normal conditions; 2) "treated" – indicated libraries made from plants subjected to any kind of stressing; 3) "low-level" indicated clone libraries prepared from genomic DNA, not on mRNA; 4) "undefined" – indicated clone libraries whose origin could not be deduced with the available information. The resulting base AT Library Registry was presented by a Microsoft Excel workbook consisting of four worksheets, one for each type of clone library class as mentioned above. The total number of sequences that were derived from clone libraries included in AT Library Registry was 113 023 ESTs.

[000117] A round of CDD was conducted when we found quantitative percentages of transcription pools volumes of plants exposed to stress conditions and plants grew in normal physiological conditions. Statistical analysis of expression spectra has revealed the quantitatively reliable differences among plants exposed to salt (hyperosmotic) stresses. The results are presented in Table 3. The conditions for comparing the clusters compared EST's from stress-induced Arabidopsis to normal plants contained EST's expressed in stress-exposed plants. Genes (clusters) of interest demonstrated to be associated with Arabidopsis stress conditions were At.11290 (glutathione S-transferase), At.5388 (lti30) and At.20845 (COR15 polypeptide).

Table III Sequences of clusters differentially expressed under salt stress conditions.

Cluster ID	Gene presented by cluster	All	Protein	Target	Background
		sequences	sequences	sequences	sequences
At.5801	Arabidopsis thaliana AT3g28220/T19D11_3 mRNA, complete cds	10	2	7	1
At.5388	Arabidopsis thaliana (Landsberg Erecta) lti30 mRNA	13	3	8	1
At.11290	Arabidopsis thaliana chromosome I glutathione S-transferase (GST30) mRNA, complete cds	13	3	8	2
At.12464	Arabidopsis thaliana chromosome II section 206 of 255 of the complete sequence. Sequence from clones F16M14	13	1	11	1
AL20845	Arabidopsis thaliana mRNA for COR15 polypeptide	32	4	24	4

[00118] The methods of the present invention are also applicable to other agricultural plants that are well represented in the UniGene database. For example, as of 20 November 2001, there were 34812 sequences in 4012 clusters for Hordeum vulgare, 47841 sequences in 12836 clusters for Oryza sativa, 31826 sequences in 2744 clusters for Triticum aestivum and 69231 sequences in 7171 clusters for Zea mays. Furthermore, the methods of the present invention may be applied to other organisms additional datasets are developed that build clusters similar to UniGene database. There are 208198 sequences available for Glycine max, 141687 sequences for Lycopersicon esculentum, 137588 sequences for Medicago truncatula, 76645 sequences for Sorghum bicolor and 55637 sequences for Solanum tuberosum. Since about 113 000 sequences were enough to obtain 10 statistically reliable results in our investigation it is reasonable to recommend using of CDD method for searching for stress-induced genes in the above mentioned plants as done with Arabidopsis. [000119] The investigation of Arabidopsis thaliana associated ESTs derived from clone libraries made from the stress-exposed and normal plants revealed three genes that encoded proteins that were overexpressed-in-stress proteins (as used herein, the term "stress-overexpressed applies to 15 the fact that 80% or more of the sequences from their clusters are derived from plant grown in stress conditions. The available clone libraries were also adequate for investigation of salt-induced stress. Thus, seven of eight total ESTs in cluster AT.5801 were derived from library m27 made from 10-14-days old shoots treated by 160mM NaCl solution for several hours. Eight of a total of nine ESTs of cluster At.11290 are also derived from this clone library. Cluster At.20845 consists of 20 22 ESTs from the same clone library 27, 2 ESTs from the plant parts treated by 200 mM NaCl (library numbers 15 and 40) and 4 ESTs from the parts of normal plant. Library 27 was deliberately enriched by sequences specifically expressed in salt stressed plant whereas libraries 15 and 40 were not as can bee seen quite clearly from the typical stress-induced cluster structures (as e.g., At.20845). It is clear also that the CDD methods of the present invention are more productive than 25 an experimental approach which is not sensitive enough to distinguish between low levels of expression of salt-induced genes.

[000120] One of the revealed clusters At.11290 represented the glutathione-S-transferase gene (GST30). It is known that glutathione transferases are involved in different stress-induced pathways. For example the expression of one of these transferases is increasing the plant's resistance for the aluminum abundance. Moreover, it was shown that such plants are display a

significant increase of oxidative stress resistance which can be seen when straining the plant's roots with H(2)DCFDA (Ezalki B. et al., 2001 Plant Physiol 2001 Nov;127(3):918-927). It is also known that the induction of glutathione-S-transferases occurs when the plant is infected with Peronospora parasitica or Pseudomonas syringae pv. Tomato, when the plant is treated by some kind of herbicides and even when the leaf structure is broken (Rairdan GJ et al., 2001 Mol Plant Microbe Interact 2001 Oct;14(10):1235-46; Vollenweider S et al., 2000 Plant J 2000 Nov;24(4):467-76). The level of glutathione-S-transferase gene also increases when the plant cells are treated with auxine, salicylic acid or hydrogenic peroxide (Chen W. Singh KB 1999 Plant Physiol 2001 Nov;127(3):918-927). As it can be deduced from published data the glutathione-S-transferase gene is often overexpressed under different kinds of stress conditions in plants. Nevertheless as it is shown in our work, this gene is specifically expressed under salt stress conditions and may serve as marker for this kind of stress.

[000121] The other revealed cluster At.5388 represents the gene lti30 coding dehydrine lti30 which synthesis is induced under the low-temperature stress but not in plants treated by abscizic acid or drought or cold (Welin B.V. et al., 1994 Plant Mol Biol 1994 Oct;26(1):131-44). The cluster At.20845 is representing cor15 protein which shows even more cryoprotective activity than BSA or sacharose (Lin C, Thomashow MF, 1992 *Biochem Biophys Res Commun* 1992 Mar 31;183(3):1103-8). So far as both genes were revealed in our CDD experiments with salt stress-induced genes it might be reasonable to suppose a common underlying processes of regulation of the salt- and temperature-induced plant response.

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CLAIMS

What is claimed is:

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1. A method for determining whether a nucleic acid is a marker for a predetermined phenotype or cell type of interest from a biological species which comprises:

- (a) providing a database of expressed sequence tag sequences (EST's) from the species;
- (b) placing said EST's in groups termed clusters based on homology of EST's within each cluster;
- (c) determining for each cluster the total number of EST's within said cluster;
- (d) ordering said clusters sequentially based on the number of EST's in each cluster;
- (e) dividing said ordered clusters into subranges based on the number of EST's per cluster;
- (f) determining for each cluster subrange obtained from step (e) the number EST's within said cluster which are expressed in said predetermined cell type of interest;
- (g) calculating according to a normal distribution the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in said cell type of interest, wherein said threshold percentage is a percentage from about 10% to about 100%;
- (h) determining the number of clusters in each subrange observed to contain said predetermined threshold percentage of EST's expressed in said predetermined cell type; and
- (i) identifying subranges having an observed number of clusters that meet said predetermined threshold percentage greater than the number of clusters expected to meet said predetermined threshold percentage for the subrange according to normal distribution;

wherein if the percentage of EST's expressed in said cell type of interest in a cluster identified in (i) is equal to or greater than said predetermined threshold percentage, said cluster contains a nucleic acid that is a marker for the cell type of interest.

- 25 2. The method of claim 1 wherein one or more of the steps are performed on a computer.
 - 3. The method of claim 1 wherein the individual clusters are divided into subranges exponentially.

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4. The method of claim 1 wherein the individual clusters are divided into subranges linearly.

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5. The method of claim 1 wherein the predetermined threshold percentage of EST's expressed in

said cell type of interest is a percentage of about 50% to 100%.

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- 6. The method of claim 1 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of about 70% to 100%.
- 7. The method of claim 1 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of about 80% to 100%.
 - 8. The method of claim 1 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of about 90% to 100%.
- 9. The method of claim 1 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of at least 80%.
 - 10. The method of claim 1 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of at least 90%.

11. The method of claim 1 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of at least 95%.

- 12. The method of claim 1 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of 100%.
 - 13. A method as in claim 1 wherein the cell type of interest is an abnormal cell.

- 14. The method of claim 1 or claim 13 wherein step (i) comprises identifying subranges having an observed number of clusters meeting said predetermined threshold percentage at least five times greater than the number expected for the subrange according to normal distribution.
- 15. The method of claim 1 or claim 13 wherein step (i) comprises identifying subranges having an observed number of clusters meeting said predetermined threshold percentage at least one standard deviation greater than the number expected for the subrange according to normal distribution.
- 10 16. The method of claim 1 or claim 13 wherein the species is human.

- 17. The method of claim 16 wherein the individual clusters are divided into subranges exponentially.
- 15 18. The method of claim 16 wherein the individual clusters are divided into subranges exponentially.
 - 19. The method of claim 16 wherein the predetermined threshold percentage of EST's expressed in a tumor cell is at least 90%.
 - 20. The method of claim 16 wherein the predetermined threshold percentage of EST's expressed in a tumor cell is 95%.
- 21. The method of claim 16 wherein the predetermined threshold percentage of EST's expressed in a tumor cell is 100%.
 - 22. A method for determining the progression of colon cancer in a human which comprises determining the level of expression of guanylate cyclase 2C in a cell, wherein if the level of

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guanylate cyclase 2C expression is greater than the level of expression of guanylate cyclase 2C in normal cells, said cell is a tumor cell.

- 23. The method of claim 22 wherein the level of the guanylate cyclase 2C is detected by
 determining the level of mRNA expression for the guanylate cyclase 2C gene.
- 24. An isolated antibody which specifically binds to a tumor-associated antigen encoded by a nucleic acid selected from the group consisting of SEQ ID NO:'s 9, 11, 13, 15, 17, 19, 23, 25, 27, 29, 33, 35, 37, 39, 41, 45, 47, 55, 57, 59, 61, 63, 65, 67, 69, 73, 75, 77, 79, 81, 83, 89, 91, 93, 95, 97, 99, 101, 103, 107, 109, 111, 113, 115, 117, 119, 121, 123, 127, 129, 131, 133, 135, 137, 138, 140, 142, 144, 146, 148, 150, 153, 155, 157, 158, 160, 162, 164, 166, 168, 172, 174, 176, 178, 180, 182, 184, 186, 189, 191, 193, 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 256, 258, 260, 262, 264, 266, 268, 270, 272, 274, 276, 278, 280, 282, 284, 286, 288, 290, 292, 294, 296, 298, 300, 302, 304, 306, 308, 310, 312, 314, 316, 318, 320, 322, 324, 326, 328, 330, 332, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412 and 414.
- 25. An isolated antibody as in claim 24 wherein the nucleic acid is encoded by a sequence selected from the group consisting of SEQ ID NO:'s 73, 184, 186 and 242.
 - 26. An isolated antibody as in claim 24 which further comprises a toxin.
- 27. A method for detecting a tumor cell which comprises detecting the expression in said cell of a tumor-associated marker, wherein said marker is a nucleic acid selected from the group of nucleic acids in claim 24.

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- 28. A method as in claim 27 wherein the nucleic acid marker is selected from the group consisting of SEQ ID NO:'s 73, 184, 186 and 242.
- 29. A method for detecting a tumor cell which comprises detecting the expression in said cell of a tumor-associated marker, wherein said marker is a polypeptide selected from the group consisting of SEQ ID NO:'s 10, 12, 14,16, 20, 24, 46, 28, 30, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 71, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 124, 126, 128, 130, 132, 134, 136, 139, 141, 143, 145, 147, 149, 151, 152, 154, 156, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 231, 233, 235, 237, 239, 241, 243, 247, 249, 251, 253, 255, 257, 259, 261, 263, 265, 267, 269, 271, 273, 275, 277, 279, 281, 283, 285, 287, 289, 291, 293, 295, 297, 299, 301, 303, 305, 307, 309, 311, 313, 315, 317, 319, 321, 323, 325, 327, 329, 331, 333, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 379, 381, 383, 385, 387, 389, 391, 393, 397, 399, 401, 403, 405, 407, 409, 411, 413 and 415.
 - 30. A method as in claim 29 wherein the polypeptide marker is selected from the group consisting of sequence selected from the group consisting of SEQ ID NO:'s 74, 185, 187, 188 and 243.
- 31. A method for regulating the growth of a tumor cell which comprises altering the level of expression of a tumor-associated marker, wherein said marker is a nucleic acid selected from the group of nucleic acids of claim 24.
- 32. A method as in claim 31 wherein the nucleic acid marker is selected from the group consisting of sequences selected from the group consisting of SEQ ID NO:'s 73, 184, 186 and 242.
 - 33. A method as in claim 31 wherein the level of expression of the tumor-associated marker is regulated with an siRNA.

34. A method for regulating the growth of a tumor cell which comprises altering the level of expression of a tumor marker, wherein said marker is a polypeptide selected from the group of polypeptides of claim 29.

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- 35. A method as in claim 34 wherein the polypeptide is selected from the group consisting of sequence selected from the group consisting of SEQ ID NO:'s 74, 185, 187, 188 and 243.
- 36. A method for preventing the growth of a tumor cell which comprises treating the cell with an antibody specific for a tumor-associated antigen wherein the antigen comprises a polypeptide as in claim 29.
 - 37. A method as in claim 34 wherein the tumor marker is a polypeptide selected from the polypeptides of SEQ ID NO:'s 74, 185, 187, 188 and 242.

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- 38. A method as in claims 36 or 37 wherein said antibody further comprises a toxin.
- 39. An isolated polypeptide for use as an immunogen, wherein said polypeptide is selected from the group of polypeptides of claim 29.

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- 39. The isolated peptide of claim 37 or 38 which comprises an epitope reactive with a Cytotoxic T-cell.
- 40. A method for determining whether a nucleic acid is a marker for a stress-induced phenotype in a species which comprises:
 - (a) providing a database of expressed sequence tag sequences (EST's) from the species;
 - (b) placing said EST's in groups termed clusters based on homology of EST's within each cluster;

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- (c) determining for each cluster the total number of EST's within said cluster;
- (d) ordering said clusters sequentially based on the number of EST's in each cluster;
- (e) dividing said ordered clusters into subranges based on the number of EST's per cluster;
- (f) determining for each cluster subrange obtained from step (e) the number EST's within said cluster which are expressed in a cell under said stress conditions;
- (g) calculating according to a normal distribution the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in a cell under said stress conditions, wherein said threshold percentage is a percentage from about 10% to about 80%;
- (h) determining the number of clusters in each subrange observed to contain said predetermined threshold percentage of EST's expressed in said cell; and
- (i) identifying subranges having an observed number of clusters that meet said predetermined threshold percentage greater than the number of clusters expected to meet said predetermined threshold percentage for the subrange according to normal distribution;

wherein if the percentage of EST's expressed in said cell type of interest in a cluster identified in (i) is equal to or greater than said predetermined threshold percentage, said cluster contains a nucleic acid marker that is a marker for the stress-induced phenotype.

- 41. The method of claim 40 wherein one or more of the steps are performed on a computer.
- 20 42. The method of claim 40 wherein the individual clusters are divided into subranges exponentially.
 - 43. The method of claim 40 wherein the individual clusters are divided into subranges linearly.
- 44. The method of claim 40 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of about 80%.
 - 45. The method of claim 40 wherein the species is Arabdopsis.

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- 46. The method of claims 40 or 45 wherein the stress-induced phenotype is selected from the group consisting of hyperosmotic stress and high salt conditions.
- 47. A method for determining whether a nucleic acid is a marker for a tumor cell from a human which comprises:
 - (a) providing a database of expressed sequence tag sequences (EST's) from human tumor cells and human normal cells;
 - (b) placing said EST's in groups termed clusters based on homology of EST's within each cluster;
 - (c) determining for each cluster the total number of EST"s within said cluster;
 - (d) ordering said clusters sequentially based on the number of EST's in each cluster;
 - (e) dividing said ordered clusters into subranges based on the number of EST's per cluster;
- (f) determining for each cluster subrange obtained from step (e) the number EST's within said cluster which are expressed in a tumor cell;
 - (g) calculating according to a normal distribution the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in said human tumor cells, wherein said threshold percentage is a percentage from about 10% to about 100%;
 - (h) determining the number of clusters in each subrange observed to contain said predetermined threshold percentage of EST's expressed in a tumor cell; and
 - (i) identifying subranges having an observed number of clusters that meet said predetermined threshold percentage greater than the number of clusters expected to meet said predetermined threshold percentage for the subrange according to normal distribution;

wherein if the percentage of EST's expressed in said cell type of interest in a cluster identified in (i) is equal to or greater than said predetermined threshold percentage, said cluster contains a nucleic acid that is a marker for a tumor cell.

48. The method of claim 47 wherein one or more of the steps are performed on a computer.

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- 49. The method of claim 47 wherein the individual clusters are divided into subranges exponentially.
- 50. The method of claim 47 wherein the individual clusters are divided into subranges linearly.

- 51. The method of claim 47 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of about 80% to 100%.
- 52. The method of claim 47 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of at least 90%.
 - 53. The method of claim 47 wherein the predetermined threshold percentage of EST's expressed in said cell type of interest is a percentage of 100%.
- 54. The method of claim 47 wherein step (i) comprises identifying subranges having an observed number of clusters meeting said predetermined threshold percentage at least five times greater than the number expected for the subrange according to normal distribution.
- 55. The method of claim 47 wherein step h consists of (i) identifying subranges having an observed number of clusters meeting said predetermined threshold percentage at least one standard deviation greater than the number expected for the subrange according to normal distribution.

SEQUENCE LISTING

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 - Thr Gln Ala Lys Leu Leu Ala Lys Lys Arg Val Val Arg Met Leu Leu 325 330 335
- Val Ile Val Val Leu Phe Phe Leu Cys Trp Leu Pro Val Tyr Ser Ala 340 345 350
- Asn Thr Trp Arg Ala Phe Asp Gly Pro Gly Ala His Arg Ala Leu Ser 355 360 365
- Gly Ala Pro Ile Ser Phe Ile His Leu Leu Ser Tyr Ala Ser Ala Cys 370 375 380
- Val Asn Pro Leu Val Tyr Cys Phe Met His Arg Arg Phe Arg Gln Ala 385 390 395 400
- Cys Leu Glu Thr Cys Ala Arg Cys Cys Pro Arg Pro Pro Arg Ala Arg 405 410 415
- Pro Arg Ala Leu Pro Asp Glu Asp Pro Pro Thr Pro Ser Ile Ala Ser 420 425 430
- Leu Ser Arg Leu Ser Tyr Thr Thr Ile Ser Thr Leu Gly Pro Gly 435 440 445

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<212> PRT

<213> Homo sapiens

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Ile Ala Ala Ser Ser Thr Tyr His Gln His Gln Gln Pro Pro Ser Gly 20 25 30 .

Gly Gly Ala Gly Pro Gly Gly Asn Ser Ser Ser Ser Ser Ser Leu His $35 \hspace{1cm} 40 \hspace{1cm} 45$

Lys Pro Gln Glu Ser Pro Thr Leu Pro Val Ser Thr Ala Thr Asp Ser 50 55 60

Ser Tyr Tyr Thr Asn Gln Gln His Pro Ala Gly Gly Gly Gly Gly 65 70 75 80

Gly Ser Pro Tyr Ala His Met Gly Ser Tyr Gln Tyr Gln Ala Ser Gly
85 90 95

Leu Asn Asn Val Pro Tyr Ser Ala Lys Ser Ser Tyr Asp Leu Gly Tyr
100 105 110

Thr Ala Ala Tyr Thr Ser Tyr Ala Pro Tyr Gly Thr Ser Ser Pro 115 120 125 \P

- Ala Asn Asn Glu Pro Glu Lys Glu Asp Leu Glu Pro Glu Ile Arg Ile 130 135 140
- Val Asn Gly Lys Pro Lys Lys Val Arg Lys Pro Arg Thr Ile Tyr Ser 145 150 155 160
- Ser Phe Gln Leu Ala Ala Leu Gln Arg Arg Phe Gln Lys Thr Gln Tyr 165 170 175
- Leu Ala Leu Pro Glu Arg Ala Glu Leu Ala Ala Ser Leu Gly Leu Thr 180 185 190
- Gln Thr Gln Val Lys Ile Trp Phe Gln Asn Arg Arg Ser Lys Phe Lys 195 200 205
- Lys Met Trp Lys Ser Gly Glu Ile Pro Ser Glu Gln His Pro Gly Ala 210 215 220
- Ser Ala Ser Pro Pro Cys Ala Ser Pro Pro Val Ser Ala Pro Ala Ser 225 230 235 240
- Trp Asp Phe Gly Val Pro Gln Arg Met Ala Gly Gly Gly Pro Gly 245 250 255
- Ser Gly Gly Ser Gly Ala Gly Ser Ser Gly Ser Ser Pro Ser Ser Ala 260 265 270
- Ala Ser Ala Phe Leu Gly Asn Tyr Pro Trp Tyr His Gln Thr Ser Gly 275 280 285
- Ser Ala Ser His Leu Gln Ala Thr Ala Pro Leu Leu His Pro Thr Gln 290 295 300
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WO 02/103028 PCT/IB02/04189 (. .

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Arg Lys Glu Ala Cys Leu Leu Tyr Glu Ile Lys Trp Gly Met Ser Arg 35 40 45

9

Lys Ile Trp Arg Ser Ser Gly Lys Asn Thr Thr Asn His Val Glu Val

Asn Phe Ile Lys Lys Phe Thr Ser Glu Arg Asp Phe His Pro Ser Met 70

Ser Cys Ser Ile Thr Trp Phe Leu Ser Trp Ser Pro Cys Trp Glu Cys 90 85

Ser Gln Ala Ile Arg Glu Phe Leu Ser Arg His Pro Gly Val Thr Leu 105

Val Ile Tyr Val Ala Arg Leu Phe Trp His Met Asp Gln Gln Asn Arg

Gln Gly Leu Arg Asp Leu Val Asn Ser Gly Val Thr Ile Gln Ile Met 135

Arg Ala Ser Glu Tyr Tyr His Cys Trp Arg Asn Phe Val Asn Tyr Pro 150

Pro Gly Asp Glu Ala His Trp Pro Gln Tyr Pro Pro Leu Trp Met Met

Leu Tyr Ala Leu Glu Leu His Cys Ile Ile Leu Ser Leu Pro Pro Cys 185

Leu Lys Ile Ser Arg Arg Trp Gln Asn His Leu Thr Phe Phe Arg Leu

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Ala Ala Asp Leu His Lys Asn Glu Trp Asn Ala Tyr Tyr Glu Glu Val 50 55 60

Val Tyr Val Leu Glu Glu Ile Glu Tyr Met Ile Gln Lys Leu Pro Glu 65 70 75 80

Trp Ala Ala Asp Glu Pro Val Glu Lys Thr Pro Gln Thr Gln Gln Asp . 85 90 95

Glu Leu Tyr Ile His Ser Glu Pro Leu Gly Val Val Leu Val Ile Gly 100 105 110

Thr Trp Asn Tyr Pro Phe Asn Leu Thr Ile Gln Pro Met Val Gly Ala 115 120 125

Ile Ala Ala Gly Asn Ala Val Val Leu Lys Pro Ser Glu Leu Ser Glu 130 135 140

Asn Met Ala Ser Leu Leu Ala Thr Ile Ile Pro Gln Tyr Leu Asp Lys 145 150 155 160

Asp Leu Tyr Pro Val Ile Asn Gly Gly Val Pro Glu Thr Thr Glu Leu 165 170 175

Leu Lys Glu Arg Phe Asp His Ile Leu Tyr Thr Gly Ser Thr Gly Val

Gly Lys Ile Ile Met Thr Ala Ala Ala Lys His Leu Thr Pro Val Thr

' **--**

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195 200 205

WO 02/103028

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Gly Gln Thr Cys Val Ala Pro Asp Tyr Ile Leu Cys Asp Pro Ser Ile 245 250 255

Gln Asn Gln Ile Val Glu Lys Leu Lys Lys Ser Leu Lys Glu Phe Tyr 260 265 270

Gly Glu Asp Ala Lys Lys Ser Arg Asp Tyr Gly Arg Ile Ile Ser Ala 275 280 285

Arg His Phe Gln Arg Val Met Gly Leu Ile Glu Gly Gln Lys Val Ala 290 295 300

Tyr Gly Gly Thr Gly Asp Ala Ala Thr Arg Tyr Ile Ala Pro Thr Ile 305 310 315 320

Leu Thr Asp Val Asp Pro Gln Ser Pro Val Met Gln Glu Glu Ile Phe 325 330 335

Gly Pro Val Leu Pro Ile Val Cys Val Arg Ser Leu Glu Glu Ala Ile 340 345 350

Gln Phe Ile Asn Gln Arg Glu Lys Pro Leu Ala Leu Tyr Met Phe Ser 355 360 365

Ser Asn Asp Lys Val Ile Lys Lys Met Ile Ala Glu Thr Ser Ser Gly 370 380

Gly Val Ala Ala Asn Asp Val Ile Val His Ile Thr Leu His Ser Leu 385 390 395 400

Pro Phe Gly Gly Val Gly Asn Ser Gly Met Gly Ser Tyr His Gly Lys 405 410 415

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Glu Pro Leu Lys Asn Leu Glu Asp Ala Val Asn Glu Gly Leu Glu Ile 50 55

Val Arg Gly Arg Leu Gln Asn Ala Gly Leu Asn Val Thr Val Asn Ala

<211> 1073 <211> PRT <213> Homo sapiens

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- Ser Ser Thr Cys Glu Gly Leu Asp Leu Leu Arg Lys Ile Ser Asn Ala 100 105 110
- Gln Arg Met Gly Cys Val Leu Ile Gly Pro Ser Cys Thr Tyr Ser Thr $115~_{\mbox{\sc V}}$
- Phe Gln Met Tyr Leu Asp Thr Glu Leu Ser Tyr Pro Met Ile Ser Ala 130 135 140
- Gly Ser Phe Gly Leu Ser Cys Asp Tyr Lys Glu Thr Leu Thr Arg Leu 145 150 155 160
- Met Ser Pro Ala Arg Lys Leu Met Tyr Phe Leu Val Asn Phe Trp Lys 165 170 175
- Thr Asn Asp Leu Pro Phe Lys Thr Tyr Ser Trp Ser Thr Ser Tyr Val 180 185 190
- Tyr Lys Asn Gly Thr Glu Thr Glu Asp Cys Phe Trp Tyr Leu Asn Ala 195 200 205
- Leu Glu Ala Ser Val Ser Tyr Phe Ser His Glu Leu Gly Phe Lys Val 210 215 220
- Val Leu Arg Gln Asp Lys Gl'u Phe Gln Asp Ile Leu Met Asp His Asn 225 230 235 240
- Arg Lys Ser Asn Val Ile Ile Met Cys Gly Gly Pro Glu Phe Leu Tyr 245 250 255
- Lys Leu Lys Gly Asp Arg Ala Val Ala Glu Asp Ile Val Ile Ile Leu 260 265 270
- Val Asp Leu Phe Asn Asp Gln Tyr Leu Glu Asp Asn Val Thr Ala Pro 275 280 285
- Asp Tyr Met Lys Asn Val Leu Val Leu Thr Leu Ser Pro Gly Asn Ser 290 295 300

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Val Ile Leu Lys Asp Leu Lys His Asn Asp Gly Asn Phe Thr Glu Lys

18

520

515

Gln Lys Ile Glu Leu Asn Lys Leu Leu Gln Ile Asp Tyr Tyr Asn Leu 530 540

Thr Lys Phe Tyr Gly Thr Val Lys Leu Asp Thr Met Ile Phe Gly Val 545 550 555 560

Ile Glu Tyr Cys Glu Arg Gly Ser Leu Arg Glu Val Leu Asn Asp Thr 565 570 575

Ile Ser Tyr Pro Asp Gly Thr Phe Met Asp Trp Glu Phe Lys Ile Ser 580 585 590

Val Leu Tyr Asp Ile Ala Lys Gly Met Ser Tyr Leu His Ser Ser Lys 595 600 605

Thr Glu Val His Gly Arg Leu Lys Ser Thr Asn Cys Val Val Asp Ser 610 615 620

Arg Met Val Val Lys Ile Thr Asp Phe Gly Cys Asn Ser Ile Leu Pro 625 630 635 640

Pro Lys Lys Asp Leu Trp Thr Ala Pro Glu His Leu Arg Gln Ala Asn 645 650 655

Ile Ser Gln Lys Gly Asp Val Tyr Ser Tyr Gly Ile Ile Ala Gln Glu 660 665 670

Ile Ile Leu Arg Lys Glu Thr Phe Tyr Thr Leu Ser Cys Arg Asp Arg 675 680 685

Asn Glu Lys Ile Phe Arg Val Glu Asn Ser Asn Gly Met Lys Pro Phe 690 695 700

Arg Pro Asp Leu Phe Leu Glu Thr Ala Glu Glu Lys Glu Leu Glu Val 715 720

Tyr Leu Leu Val Lys Asn Cys Trp Glu Glu Asp Pro Glu Lys Arg Pro 725 730 735

Asp Phe Lys Lys Ile Glu Thr Thr Leu Ala Lys Ile Phe Gly Leu Phe 740 745 750

His Asp Gln Lys Asn Glu Ser Tyr Met Asp Thr Leu Ile Arg Arg Leu 755 760 765

- Gln Leu Tyr Ser Arg Asn Leu Glu His Leu Val Glu Glu Arg Thr Gln
 770 780
- Leu Tyr Lys Ala Glu Arg Asp Arg Ala Asp Arg Leu Asn Phe Met Leu 785 790 795 800
- Leu Pro Arg Leu Val Val Lys Ser Leu Lys Glu Lys Gly Phe Val Glu 805 810 815
- Pro Glu Leu Tyr Glu Glu Val Thr Ile Tyr Phe Ser Asp Ile Val Gly 820 825 830
- Phe Thr Thr Ile Cys Lys Tyr Ser Thr Pro Met Glu Val Val Asp Met 835 840 845
- Leu Asn Asp Ile Tyr Lys Ser Phe Asp His Ile Val Asp His His Asp 850 855 860
- Val Tyr Lys Val Glu Thr Ile Gly Asp Ala Tyr Met Val Ala Ser Gly 865 870 875 880
- Leu Pro Lys Arg Asn Gly Asn Arg His Ala Ile Asp Ile Ala Lys Met 885 890 895
- Ala Leu Glu Ile Leu Ser Phe Met Gly Thr Phe Glu Leu Glu His Leu 900 905 910
- Pro Gly Leu Pro Ile Trp Ile Arg Ile Gly Val His Ser Gly Pro Cys 915 920 925
- Ala Gly Val Val Gly Ile Lys Met Pro Arg Tyr Cys Leu Phe Gly 930 935 940
- Asp Thr Val Asn Thr Ala Ser Arg Met Glu Ser Thr Gly Leu Pro Leu 945 950 955 960
- Arg Ile His Val Ser Gly Ser Thr Ile Ala Ile Leu Lys Arg Thr Glu 965 970 975

Cys Gln Phe Leu Tyr Glu Val Arg Gly Glu Thr Tyr Leu Lys Gly Arg 980 985 990

Gly Asn Glu Thr Thr Tyr Trp Leu Thr Gly Met Lys Asp Gln Lys Phe 995 1000 1005

Asn Leu Pro Thr Pro Pro Thr Val Glu Asn Gln Gln Arg Leu Gln 1010 1015 1020

Ala Glu Phe Ser Asp Met Ile Ala Asn Ser Leu Gln Lys Arg Gln 1025 1030 1035

Ala Ala Gly Ile Arg Ser Gln Lys Pro Arg Arg Val Ala Ser Tyr 1040 1045 1050

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<213> Homo sapiens

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Asp Arg Tyr Leu Leu Lys Ala Leu Asp Lys Tyr Trp His Glu Asp Cys

Leu Lys Cys Ala Cys Cys Asp Cys Arg Leu Gly Glu Val Gly Ser Thr

Leu Tyr Thr Lys Ala Asn Leu Ile Leu Cys Arg Arg Asp Tyr Leu Arg

Leu Phe Gly Thr Thr Gly Asn Cys Ala Ala Cys Ser Lys Leu Ile Pro

Ala Phe Glu Met Val Met Arg Ala Arg Asp Asn Val Tyr His Leu Asp 105

Cys Phe Ala Cys Gln Leu Cys Asn Gln Arg Phe Cys Val Gly Asp Lys 115 120 125

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Gln Leu Arg Pro Ala Ala Asp Gly Gln Pro Ser Gly Gly Gly His Lys 65 70 75 80

Ser Ala Pro Lys Gln Val Lys Arg Gln Arg Ser Ser Ser Pro Glu Leu 85 90 95

Met Arg Cys Lys Arg Arg Leu Asn Phe Ser Gly Phe Gly Tyr Ser Leu 100 105 110

Pro Gln Gln Gln Pro Ala Ala Val Ala Arg Arg Asn Glu Arg Glu Arg 115 120 125

Asn Arg Val Lys Leu Val Asn Leu Gly Phe Ala Thr Leu Arg Glu His 130 135 140

Val Pro Asn Gly Ala Ala Asn Lys Lys Met Ser Lys Val Glu Thr Leu 145 150 155 160

Arg Ser Ala Val Glu Tyr Ile Arg Ala Leu Gln Gln Leu Leu Asp Glu 165 170 175

His Asp Ala Val Ser Ala Ala Phe Gln Ala Gly Val Leu Ser Pro Thr 180 185 190

Ile Ser Pro Asn Tyr Ser Asn Asp Leu Asn Ser Met Ala Gly Ser Pro 195 200 205

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26

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Leu Ala His Ser Arg Ala Ala Ala Ala Ala Ala Val Ala Ala Ala Thr 35 40 45

Ala Ala Val Glu Gly Ser Gly Gly Ser Gly Gly Ser His His 50 55 60

His Gln Ser Arg Gly Ala Cys Thr Ser His Asp Pro Gln Ser Ser Arg 65 70 75 80

- Gly Ser Arg Arg Arg Arg Gln Arg Ser Glu Lys Lys Lys Ala His
 85 90 95
- Tyr Arg Gln Ser Ser Phe Pro His Cys Ser Asp Leu Met Pro Ser Gly
 100 105 110
- Ser Glu Glu Lys Ile Leu Arg Glu Leu Ser Glu Glu Glu Glu Asp Glu 115 120 125
- Glu Glu Glu Glu Glu Glu Glu Glu Gly Arg Phe Tyr Tyr Ser Glu 130 135 140
- Asp Asp His Gly Asp Glu Cys Ser Tyr Thr Asp Leu Leu Pro Gln Asp 145 150 155 160
- Glu Gly Gly Gly Tyr Ser Ser Val Arg Tyr Ser Asp Cys Cys Glu 165 170 175
- Arg Val Val Ile Asn Val Ser Gly Leu Arg Phe Glu Thr Gln Met Lys 180 185 190
- Thr Leu Ala Gln Phe Pro Glu Thr Leu Leu Gly Asp Pro Glu Lys Arg 195 200 205
- Thr Gln Tyr Phe Asp Pro Leu Arg Asn Glu Tyr Phe Phe Asp Arg Asn 210 215 220
- Arg Pro Ser Phe Asp Ala Ile Leu Tyr Tyr Tyr Gln Ser Gly Gly Arg 225 230 235 240
- Leu Lys Arg Pro Val Asn Val Pro Phe Asp Ile Phe Thr Glu Glu Val 245 250 255
- Lys Phe Tyr Gln Leu Gly Glu Glu Ala Leu Leu Lys Phe Arg Glu Asp 260 265 270
- Glu Gly Phe Val Arg Glu Glu Glu Asp Arg Ala Leu Pro Glu Asn Glu 275 280 285

Phe Lys Lys Gln Ile Trp Leu Leu Phe Glu Tyr Pro Glu Ser Ser Ser 290 295 300

Pro Ala Arg Gly Ile Ala Ile Val Ser Val Leu Val Ile Leu Ile Ser 305 310 315 320

Ile Val Ile Phe Cys Leu Glu Thr Leu Pro Glu Phe Arg Asp Arg 325 330 335

Asp Leu Val Met Ala Leu Ser Ala Gly Gly His Gly Gly Leu Leu Asn 340 345 350

Asp Thr Ser Ala Pro His Leu Glu Asn Ser Gly His Thr Ile Phe Asn 355 360 365

Asp Pro Phe Phe Ile Val Glu Thr Val Cys Ile Val Trp Phe Ser Phe 370 375 380

Glu Phe Val Val Arg Cys Phe Ala Cys Pro Ser Gln Ala Leu Phe Phe 385 390 395 400

Lys Asn Ile Met Asn Ile Ile Asp Ile Val Ser Ile Leu Pro Tyr Phe 405 410 415

Ile Thr Leu Gly Thr Asp Leu Ala Gln Gln Gln Gly Gly Gly Asn Gly 420 425 430

Gln Gln Gln Ala Met Ser Phe Ala Ile Leu Arg Ile Ile Arg Leu 435 440 445

Val Arg Val Phe Arg Ile Phe Lys Leu Ser Arg His Ser Lys Gly Leu 450 455 460

Gln Ile Leu Gly His Thr Leu Arg Ala Ser Met Arg Glu Leu Gly Leu 465 470 475 480

Leu Ile Phe Phe Leu Phe Ile Gly Val Ile Leu Phe Ser Ser Ala Val
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Tyr Phe Ala Glu Ala Asp Glu Pro Thr Thr His Phe Gln Ser Ile Pro 500 505 510

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Ser	Asn	Phe	Asn	Tyr 565	Phe	Tyr	His	Arg	Glu .570	Thr	Glu	Asn	Glu	Glu 575	Gln	
Thr	Gln	Leu	Thr 580	Gln	Asn	Ala	Val	Ser 585	Cys	Pro	Tyr	Leu	Pro 590	Ser	Asn	
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Gln Lys Ile Thr Tyr Arg Ile Ser Gly Val Gly Ile Asp Gln Pro Pro 85 90 95

Phe Gly Ile Phe Val Val Asp Lys Asn Thr Gly Asp Ile Asn Ile Thr 100 105 110

Ala Ile Val Asp Arg Glu Glu Thr Pro Ser Phe Leu Ile Thr Cys Arg 115 120 125

Ala Leu Asn Ala Gln Gly Leu Asp Val Glu Lys Pro Leu Ile Leu Thr 130 135 140

Val Lys Ile Leu Asp Ile Asn Asp Asn Pro Pro Val Phe Ser Gln Gln 145 150 155 160

Ile Phe Met Gly Glu Ile Glu Glu Asn Ser Ala Ser Asn Ser Leu Val 165 170 175

Met Ile Leu Asn Ala Thr Asp Ala Asp Glu Pro Asn His Leu Asn Ser 180 185 190

Lys Ile Ala Phe Lys Ile Val Ser Gln Glu Pro Ala Gly Thr Pro Met
195 200 205

Phe Leu Leu Ser Arg Asn Thr Gly Glu Val Arg Thr Leu Thr Asn Ser 210 215 220

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Asp Lys Asp Gly Glu Gly Leu Ser Thr Gln Cys Glu Cys Asn Ile Lys 245 250 255

Val Lys Asp Val Asn Asp Asn Phe Pro Met Phe Arg Asp Ser Gln Tyr 260 . 265 270

Ser Ala Arg Ile Glu Glu Asn Ile Leu Ser Ser Glu Leu Leu Arg Phe . 275 280 285

Gln Val Thr Asp Leu Asp Glu Glu Tyr Thr Asp Asn Trp Leu Ala Val 290 295 300

Tyr Phe Phe Thr Ser Gly Asn Glu Gly Asn Trp Phe Glu Ile Gln Thr 305 310 315 320

Asp Pro Arg Thr Asn Glu Gly Ile Leu Lys Val Val Lys Ala Leu Asp 325 330 335

Tyr Glu Gln Leu Gln Ser Val Lys Leu Ser Ile Ala Val Lys Asn Lys 340 345 350

Ala Glu Phe His Gln Ser Val Ile Ser Arg Tyr Arg Val Gln Ser Thr 355 360 365

Pro Val Thr Ile Gln Val Ile Asn Val Arg Glu Gly Ile Ala Phe Arg 370 375 380

Pro Ala Ser Lys Thr Phe Thr Val Gln Lys Gly Ile Ser Ser Lys Lys 385 390 395 400

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420 425 430

Gly Tyr Leu Met Ile Asp Ser Lys Thr Ala Glu Ile Lys Phe Val Lys 435 440 445

Asn Met Asn Arg Asp Ser Thr Phe Ile Val Asn Lys Thr Ile Thr Ala 450 455 460

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Val Tyr Val Arg Val Pro Asp Phe Asn Asp Asn Cys Pro Thr Ala Val · 485 490 495

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- Glu Asp Gln Pro Val Lys Leu Pro Ala Val Trp Ser Ile Thr Thr Leu 530 540
- Asn Ala Thr Ser Ala Leu Leu Arg Ala Gln Glu Gln Ile Pro Pro Gly 545 550 560
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- Glu Met Pro Arg Ser Leu Thr Leu Glu Val Cys Gln Cys Asp Asn Arg
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- Gly Arg Pro His Ser Gly Arg Leu Gly Pro Ala Ala Ile Gly Leu Leu 610 615 620
- Leu Leu Gly Leu Leu Leu Leu Leu Leu Ala Pro Leu Leu Leu Thr 625 630 635 640
- Cys Asp Cys Gly Ala Gly Ser Thr Gly Gly Val Thr Gly Gly Phe Ile 645 650 655
- Pro Val Pro Asp Gly Ser Glu Gly Thr Ile His Gln Trp Gly Ile Glu 660 665 670
- Gly Ala His Pro Glu Asp Lys Glu Ile Thr Asn Ile Cys Val Pro Pro 675 680 685
- Val Thr Ala Asn Gly Ala Asp Phe Met Glu Ser Ser Glu Val Cys Thr 690 695 700

Asn Thr Tyr Ala Arg Gly Thr Ala Val Glu Gly Thr Ser Gly Met Glu 705 710 715 720

Met Thr Thr Lys Leu Gly Ala Ala Thr Glu Ser Gly Gly Ala Ala Gly 725 730 735

Phe Ala Thr Gly Thr Val Ser Gly Ala Ala Ser Gly Phe Gly Ala Ala 740 745 750

Thr Gly Val Gly Ile Cys Ser Ser Gly Gln Ser Gly Thr Met Arg Thr 755 . 760 765

Arg His Ser Thr Gly Gly Thr Asn Lys Asp Tyr Ala Asp Gly Ala Ile 770 780

Ser Met Asn Phe Leu Asp Ser Tyr Phe Ser Gln Lys Ala Phe Ala Cys 785 790 795 800

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Asp Asn Glu Gly Ala Asp Ala Thr Gly Ser Pro Val Gly Ser Val Gly 820 825 830

Cys Cys Ser Phe Ile Ala Asp Asp Leu Asp Asp Ser Phe Leu Asp Ser 835 840 845

Leu Gly Pro Lys Phe Lys Lys Leu Ala Glu Ile Ser Leu Gly Val Asp 850 855 860

Gly Glu Gly Lys Glu Val Gln Pro Pro Ser Lys Asp Ser Gly Tyr Gly 865 870 875 880

Ile Glu Ser Cys Gly His Pro Ile Glu Val Gln Gln Thr Gly Phe Val 885 890 895

Lys Cys Gln Thr Leu Ser Gly Ser Gln Gly Ala Ser Ala Leu Ser Ala 900 905 910

Ser Gly Ser Val Gln Pro Ala Val Ser Ile Pro Asp Pro Leu Gln His 915 920 925

Gly Asn Tyr Leu Val Thr Glu Thr Tyr Ser Ala Ser Gly Ser Leu Val 930 935 940

Gln Pro Ser Thr Ala Gly Phe Asp Pro Leu Leu Thr Gln Asn Val Ile 945 950 955 960

Val Thr Glu Arg Val Ile Cys Pro Ile Ser Ser Val Pro Gly Asn Leu 965 970 975

Ala Gly Pro Thr Gln Leu Arg Gly Ser His Thr Met Leu Cys Thr Glu 980 985 990

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37

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Val Glu Val Thr Val Gly Leu Gln Leu Ile Gln Leu Ile Asn Val Asp

Glu Val Asn Gln Ile Val Thr Thr Asn Val Arg Leu Lys Gln Gln Trp

Val Asp Tyr Asn Leu Lys Trp Asn Pro Asp Asp Tyr Gly Val Lys 90

Lys Ile His Ile Pro Ser Glu Lys Ile Trp Arg Pro Asp Leu Val Leu 100 105 110

Tyr Asn Asn Ala Asp Gly Asp Phe Ala Ile Val Lys Phe Thr Lys Val 115 120 125

Leu Leu Gln Tyr Thr Gly His Ile Thr Trp Thr Pro Pro Ala Ile Phe 130 135 140

Lys Ser Tyr Cys Glu Ile Ile Val Thr His Phe Pro Phe Asp Glu Gln 145 150 155 160

Asn Cys Ser Met Lys Leu Gly Thr Trp Thr Tyr Asp Gly Ser Val Val 165 170 175

Ala Ile Asn Pro Glu Ser Asp Gln Pro Asp Leu Ser Asn Phe Met Glu 180 185 190

Ser Gly Glu Trp Val Ile Lys Glu Ser Arg Gly Trp Lys His Ser Val

Thr Tyr Ser Cys Cys Pro Asp Thr Pro Tyr Leu Asp Ile Thr Tyr His 210 215 220

Phe Val Met Gln Arg Leu Pro Leu Tyr Phe Ile Val Asn Val Ile Ile 225 230 235 240

Pro Cys Leu Leu Phe Ser Phe Leu Thr Gly Leu Val Phe Tyr Leu Pro 245 250 255

Thr Asp Ser Gly Glu Lys Met Thr Leu Ser Ile Ser Val Leu Leu Ser 260 265 270

Leu Thr Val Phe Leu Leu Val Ile Val Glu Leu Ile Pro Ser Thr Ser 275 280 285

Ser Ala Val Pro Leu Ile Gly Lys Tyr Met Leu Phe Thr Met Val Phe 290 295 . 300

Val Ile Ala Ser Ile Ile Ile Thr Val Ile Val Ile Asn Thr His His 305 310 315 320

Arg Ser Pro Ser Thr His Val Met Pro Asn Trp Val Arg Lys Val Phe 325 330 Ile Asp Thr Ile Pro Asn Ile Met Phe Phe Ser Thr Met Lys Arg Pro 345 Ser Arg Glu Lys Gln Asp Lys Lys Ile Phe Thr Glu Asp Ile Asp Ile Ser Asp Ile Ser Gly Lys Pro Gly Pro Pro Pro Met Gly Phe His Ser 375 Pro Leu Ile Lys His Pro Glu Val Lys Ser Ala Ile Glu Gly Ile Lys Tyr Ile Ala Glu Thr Met Lys Ser Asp Gln Glu Ser Asn Asn Ala Ala Ala Glu Trp Lys Tyr Val Ala Met Val Met Asp His Ile Leu Leu Gly 420 425 Val Phe Met Leu Val Cys Ile Ile Gly Thr Leu Ala Val Phe Ala Gly 440 Arg Leu Ile Glu Leu Asn Gln Gln Gly 455 <210> 29 <211> 3587 <212> DNA <213> Homo sapiens <400> 29 ggcacgaggc ccagacagag tgtccccaca ccctcctctg agacgccatg ttcaactcga 60 tgaccccacc accaatcagt agctatggcg agccctgctg tctccggccc ctccccagtc 120 agggggcccc cagtgtgggg acagaaggac tgtctggccc gcccttctgc caccaagcta 180 acctcatgtc cggccccac agttatgggc cagccagaga gaccaacagc tgcaccgagg 240 gcccactctt ttcttctccc cggagtgcag tcaagttgac caagaagcgg gcactgtcca 300 totcacctct gtcggatgcc agcctggacc tgcagacggt tatccgcacc tcacccagct 360 ccctcgtagc tttcatcaac tcgcgatgca catctccagg aggctcctac ggtcatctct 420

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Glu Gly Leu Ser Gly Pro Pro Phe Cys His Gln Ala Asn Leu Met Ser 35 40 45

Gly Pro His Ser Tyr Gly Pro Ala Arg Glu Thr Asn Ser Cys Thr Glu 50 60

Gly Pro Leu Phe Ser Ser Pro Arg Ser Ala Val Lys Leu Thr Lys Lys 65 70 75 80

Arg Ala Leu Ser Ile Ser Pro Leu Ser Asp Ala Ser Leu Asp Leu Gln 85 90 95

Thr Val Ile Arg Thr Ser Pro Ser Ser Leu Val Ala Phe Ile Asn Ser 100 105 110

Arg Cys Thr Ser Pro Gly Gly Ser Tyr Gly His Leu Ser Ile Gly Thr 115 120 125

Met Ser Pro Ser Leu Gly Phe Pro Ala Gln Met Asn His Gln Lys Gly 130 135 140

Pro Ser Pro Ser Phe Gly Val Gln Pro Cys Gly Pro His Asp Ser Ala 145 150 155 160

Arg Gly Gly Met Ile Pro His Pro Gln Ser Arg Gly Pro Phe Pro Thr 165 170 175

Cys Gln Leu Lys Ser Glu Leu Asp Met Leu Val Gly Lys Cys Arg Glu 180 185 190

Glu Pro Leu Glu Gly Asp Met Ser Ser Pro Asn Ser Thr Gly Ile Gln 195 200 205

Asp Pro Leu Leu Gly Met Leu Asp Gly Arg Glu Asp Leu Glu Arg Glu 210 215 220

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- Glu Gly Ala Met Lys Pro Gln Pro Ser Pro Gly Ala Gln Ser Ser Cys
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- Glu Glu Pro Glu Val Gly Thr Ser Met Val Gly Ser Gly Leu Asn Pro 705 710 715 720
- Tyr Met Asp Phe Pro Pro Thr Asp Thr Leu Gly Tyr Gly Gly Pro Glu 725 730 735
- Gly Ala Ala Glu Pro Tyr Gly Ala Arg Gly Pro Gly Ser Leu Pro 740 745 750
- Leu Gly Pro Gly Pro Pro Thr Asn Tyr Gly Pro Asn Pro Cys Pro Gln 755 760 765
- Gln Ala Ser Tyr Pro Asp Pro Thr Gln Glu Thr Trp Gly Glu Phe Pro 770 775 780
- Ser His Ser Gly Leu Tyr Pro Gly Pro Lys Ala Leu Gly Gly Thr Tyr 785 790 795 800
- Ser Gln Cys Pro Arg Leu Glu His Tyr Gly Gln Val Gln Val Lys Pro 805 810 815
- Glu Gln Gly Cys Pro Val Gly Ser Asp Ser Thr Gly Leu Ala Pro Cys 820 825 830
- Leu Asn Ala His Pro Ser Glu Gly Pro Pro His Pro Gln Pro Leu Phe 835 840 845
- Ser His Tyr Pro Gln Pro Ser Pro Pro Gln Tyr Leu Gln Ser Gly Pro 850 855 860
- Tyr Thr Gln Pro Pro Pro Asp Tyr Leu Pro Ser Glu Pro Arg Pro Cys 875 880
- Leu Asp Phe Asp Ser Pro Thr His Ser Thr Gly Gln Leu Lys Ala Gln 885 890 895

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- Gly Gly Arg Glu Asp Ala Pro Ala Gln Glu Pro Ser Tyr Gln Ser Pro 915 920 925
- Lys Phe Leu Gly Gly Ser Gln Val Ser Pro Ser Arg Ala Lys Ala Pro 930 935 940
- Val Asn Thr Tyr Gly Pro Gly Phe Gly Pro Asn Leu Pro Asn His Lys 945 950 955 960
- Ser Gly Ser Tyr Pro Thr Pro Ser Pro Cys His Glu Asn Phe Val Val 965 970 975
- Gly Ala Asn Arg Ala Ser His Arg Ala Ala Pro Pro Arg Leu Leu 980 985 990
- Pro Pro Leu Pro Thr Cys Tyr Gly Pro Leu Lys Val Gly Gly Thr Asn 995 1000 1005
- Pro Ser Cys Gly His Pro Glu Val Gly Arg Leu Gly Gly Gly Pro 1010 1015 1020
- Ala Leu Tyr Pro Pro Pro Glu Gly Gln Val Cys Asn Pro Leu Asp 1025 1030 1035
- Ser Leu Asp Leu Asp Asn Thr Gln Leu Asp Phe Val Ala Ile Leu 1040 1045 1050
- Asp Glu Pro Gln Gly Leu Ser Pro Pro Pro Ser His Asp Gln Arg 1055 1060 1065
- Gly Ser Ser Gly His Thr Pro Pro Pro Ser Gly Pro Pro Asn Met 1070 1080
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Gly Val Tyr Val Leu Ala Gly Ala Val Ala Arg Glu Asn Ala Gly Pro 50 55 60

Ala Ile Val Ile Ser Phe Leu Ile Ala Ala Leu Ala Ser Val Leu Ala 65 70 75 80

Gly Leu Cys Tyr Gly Glu Phe Gly Ala Arg Val Pro Lys Thr Gly Ser 85 90 95

Ala Tyr Leu Tyr Ser Tyr Val Thr Val Gly Glu Leu Trp Ala Phe Ile 100 105 110

Thr Gly Trp Asn Leu Ile Leu Ser Tyr Ile Ile Gly Thr Ser Ser Val 115 120 125

Ala Arg Ala Trp Ser Ala Thr Phe Asp Glu Leu Ile Gly Arg Pro Ile 130 135 140

Gly Glu Phe Ser Arg Thr His Met Thr Leu Asn Ala Pro Gly Val Leu 145 150 155 160

Ala Glu Asn Pro Asp Ile Phe Ala Val Ile Ile Ile Leu Ile Leu Thr 165 170 175

51

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- Leu Met Met Gln Leu Asp Gln Gly Thr Trp Val Arg Phe Ala Val Trp 580 585 590
- Met Leu Ile Gly Phe Ile Ile Tyr Phe Gly Tyr Gly Leu Trp His Ser 595 600 605
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Gln Ala Gly Ala Leu Gln Arg Ser Gln Ala Ala Pro Trp Ala Pro Ala 85 90 95

Pro Ala Met Val Trp Asp Val Pro Val Glu Glu Phe Pro Leu Arg Cys 100 105 110

Pro Leu Phe Ala Gln Gln Arg Val Pro Glu Gly Gly Pro Leu Leu Asp 115 120 125

Thr Arg Lys Asn Val Gln Ala Thr Glu Gly Arg Thr Lys Ala Pro Ala 130 135 140

Arg Leu Cys Ala Gly Glu Asn Ala Ser Thr Pro Ser Glu Pro Glu Lys 145 150 155 160

Phe Pro Gln Val Arg Arg Gln Arg Gly Ala Gly Ala Gly Glu Gly Glu 165 170 175

Phe Val Cys Gly Glu Cys Gly Lys Ala Phe Arg Gln Ser Ser Leu 180 185 190

Thr Leu His Arg Arg Trp His Ser Arg Glu Lys Ala Tyr Lys Cys Asp 195 200 205

Glu Cys Gly Lys Ala Phe Thr Trp Ser Thr Asn Leu Leu Glu His Arg 210 215 220

Arg Ile His Thr Gly Glu Lys Pro Phe Phe Cys Gly Glu Cys Gly Lys 225 230 235 240

Ala Phe Ser Cys His Ser Ser Leu Asn Val His Gln Arg Ile His Thr 245 250 255

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- Tyr Arg Cys Gly Glu Cys Gly Lys Ala Phe Asn Gln Arg Thr His Leu 290 295 300
- Thr Arg His His Arg Ile His Thr Gly Glu Lys Pro Tyr Gln Cys Gly 305 310 315 320
- Ser Cys Gly Lys Ala Phe Thr Cys His Ser Ser Leu Thr Val His Glu 325 330 335
- Lys Ile His Ser Gly Asp Lys Pro Phe Lys Cys Ser Asp Cys Glu Lys 340 345 350
- Ala Phe Asn Ser Arg Ser Arg Leu Thr Leu His Gln Arg Thr His Thr 355 360 365
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- His Ala Tyr Leu Leu Val His Arg Arg Ile His Ser Gly Glu Lys Pro 385 390 395 400
- Phe Lys Cys Asn Glu Cys Gly Lys Ala Phe Ser Ser His Ala Tyr Leu 405 410 415
- Ile Val His Arg Arg Ile His Thr Gly Glu Lys Pro Phe Asp Cys Ser 420 425 430
- Gln Cys Trp Lys Ala Phe Ser Cys His Ser Ser Leu Ile Val His Gln 435 440 445
- Arg Ile His Thr Gly Glu Lys Pro Tyr Lys Cys Ser Glu Cys Gly Arg 450 455 460
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Ser Ser Arg Leu Lys Leu His Leu Lys Ser Asp Met Ser Glu Cys Glu 35 40 45

Asn Asp Asp Pro Leu Leu Arg Ser Ala Gly Lys Val Arg Asp Ile Asn 50 55 60

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- Leu Asn Val Gly Gly Glu Thr Glu Asn Asn Gly Val Ser Lys Glu Ser 145 150 155 160
- Arg Thr Asn Val Arg Ile Val Asn Asn Ala Lys Asn Ser Phe Val Ala 165 170 175
- Ser Ser Val Pro Leu Asp Glu Asp Pro Gln Val Ile Glu Met Met Ala 180 185 190
- Asp Lys Lys Tyr Lys Glu Thr Phe Ser Ala Pro Ser Arg Ala Asn Glu 195 200 205
- Asn Val Ala Leu Lys Tyr Ser Ser Asn Arg Pro Pro Ile Ala Ser Leu 210 215 220
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- Gln Ser Lys Leu Asp Ile Lys Val Leu Gly Thr Gly Asn Leu Tyr His 245 250 255
- Arg Ser Ile Gly Lys Glu Ile Ala Lys Thr Ser Asn Lys Phe Gly Ser 260 265 270
- Leu Glu Lys Arg Thr Pro Thr Lys Cys Thr Thr Glu His Lys Leu Thr 275 280 285
- Thr Lys Cys Ser Leu Pro Gln Leu Lys Ser Pro Ala Pro Ser Ile Leu 290 295 300
- Lys Asn Arg Met Ser Asn Leu Gln Val Lys Gln Arg Pro Lys Ser Ser 305 310 315 320

Phe Leu Ala Asn Lys Gln Glu Arg Ser Ala Glu Asn Thr Ile Leu Pro 325 330 335

Glu Glu Glu Thr Val Val Gln Asn Thr Ser Ala Gly Lys Asp Pro Leu $340 \hspace{1cm} 345 \hspace{1cm} 350$

Lys Val Glu Asn Ser Gln Val Thr Val Ala Val Arg Val Arg Pro Phe 355 360 365

Thr Lys Arg Glu Lys Ile Glu Lys Ala Ser Gln Val Val Phe Met Ser 370 375 380

Gly Lys Glu Ile Thr Val Glu His Pro Asp Thr Lys Gln Val Tyr Asn 385 390 395 400

Phe Ile Tyr Asp Val Ser Phe Trp Ser Phe Asp Glu Cys His Pro His 405 410 415

Tyr Ala Ser Gln Thr Thr Val Tyr Glu Lys Leu Ala Ala Pro Leu Leu 420 425 430

Glu Arg Ala Phe Glu Gly Phe Asn Thr Cys Leu Phe Ala Tyr Gly Gln 435 440 445

Thr Gly Ser Gly Lys Ser Tyr Thr Met Met Gly Phe Ser Glu Glu Pro 450 455 460

Gly Ile Ile Pro Arg Phe Cys Glu Asp Leu Phe Ser Gln Val Ala Arg 465 470 475 480

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485 490 495

Val Tyr Asn Glu Lys Ile His Asp Leu Leu Val Cys Lys Asp Glu Asn 500 505 510

Gly Gln Arg Lys Gln Pro Leu Arg Val Arg Glu His Pro Val Tyr Gly
515 520 525

Pro Tyr Val Glu Ala Leu Ser Met Asn Ile Val Ser Ser Tyr Ala Asp 530 535 540

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Ile Gln Ser Trp Leu Glu Leu Gly Asn Lys Gln Arg Ala Thr Ala Ala

Leu Ser Thr Leu Arg Tyr Ala Asn Gln Ala Arg Leu Ile Val Asn Ile 690 695 700

Ala Lys Val Asn Glu Asp Met Asn Ala Lys Leu Ile Arg Glu Leu Lys 705 710 715 720

Ala Glu Ile Ala Lys Leu Lys Ala Ala Gln Arg Asn Ser Arg Asn Ile 725 730 735

Asp Pro Glu Arg Tyr Arg Leu Cys Arg Gln Glu Ile Thr Ser Leu Arg 740 745 750

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Trp Lys Glu Lys Phe Glu Gln Ala Glu Lys Arg Lys Leu Gln Glu Thr 770 785

Lys Glu Leu Gln Lys Ala Gly Ile Met Phe Gln Met Asp Asn His Leu 785 790 795 800

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Leu Tyr Met Ile Lys Glu Gly Thr Thr Thr Val Gly Lys Tyr Lys Pro 820 825 830

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His Cys Thr Ile Lys Asn Phe Gly Gly Thr Val Ser Ile Ile Pro Val 850 855 860

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Val Leu Arg His Gly Asp Arg Val Ile Leu Gly Gly Asp His Tyr Phe 885 890 895

Arg Phe Asn His Pro Val Glu Val Gln Lys Gly Lys Arg Pro Ser Gly 900 905 910

Arg Asp Thr Pro Ile Ser Glu Gly Pro Lys Asp Phe Glu Phe Ala Lys 915 920 925

Asn Glu Leu Leu Met Ala Gln Arg Ser Gln Leu Glu Ala Glu Ile Lys 930 935 940

Glu Ala Gln Leu Lys Ala Lys Glu Glu Met Met Gln Gly Ile Gln Ile 945 950 955 960

Ala Lys Glu Met Ala Gln Gln Glu Leu Ser Ser Gln Lys Ala Ala Tyr 965 970 975

Glu Ser Lys Ile Lys Ala Leu Glu Ala Glu Leu Arg Glu Glu Ser Gln 980 985 990

Arg Lys Lys Met Gln Glu Ile Asn Asn Gln Lys Ala Asn His Lys Ile 995 1000 1005

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- Leu Glu Thr Glu Lys Gln Lys Ile Ala Lys Glu Val Gln Ile Leu 1055 1060 1065
- Gln Gln Asn Arg Asn Arg Asp Lys Thr Phe Thr Val Gln Thr 1070 1075 1080
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- Asp Ile Ser Asp Lys Ser Ser Ser Asp Thr Ser Ile Arg Val Arg 1115 1120 1125
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- Glu Ser Lys Leu Ala Ala Met Lys Glu Leu Tyr Glu Ser Asn Gly 1145 1150
- Ser Asn Arg Gly Glu Asp Ala Phe Cys Asp Pro Glu Asp Glu Trp 1160 1165 1170
- Glu Pro Asp Ile Thr Asp Ala Pro Val Ser Ser Leu Ser Arg Arg 1175 1180 1185 .
- Arg Ser Arg Ser Leu Met Lys Asn Arg Arg Ile Ser Gly Cys Leu 1190 1195 1200

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Asp Ala Leu Gln Lys Leu Phe Glu Met Asp Ala Gln Gly Arg Val Trp

71

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- Trp Leu Lys Glu Thr Ser Ala Pro Glu Leu Val His Ile Leu Phe Lys 305 310 315 320
- Ser Leu Asn Phe Ile Leu Ala Arg Cys Pro Glu Ala Gly Leu Ala Ala 325 330 335
- Gln Val Ile Ser Pro Leu Leu Thr Pro Lys Ala Ile Asn Leu Leu Gln 340 345 350
- Ala Trp Thr Thr Ser Arg Ala Asp Trp Thr Gly Asp Glu Pro Leu Pro 370 375 380
- Tyr Gln Pro Thr Phe Ser Asp Asp Trp Gln Leu Pro Glu Pro Ser Ser 385 390 395 400
- Gln Ala Pro Leu Gly Tyr Gln Asp Pro Val Ser Leu Arg Arg Gly Ser 405 410 415
- His Arg Leu Gly Ser Thr Ser His Phe Pro Gln Glu Lys Thr His Asn 420 425 430
- His Asp Pro Gln Pro Gly Asp Pro Asn Ser Arg Pro Ser Ser Pro Lys 435 440 445
- Pro Ala Gln Pro Ala Leu Lys Met Gln Val Leu Tyr Glu Phe Glu Ala 450 455 460
- Arg Asn Pro Arg Glu Leu Thr Val Val Gln Gly Glu Lys Leu Glu Val 465 470 475 480
- Leu Asp His Ser Lys Arg Trp Trp Leu Val Lys Asn Glu Ala Gly Arg
 485 490 495
- Ser Gly Tyr Ile Pro Ser Asn Ile Leu Glu Pro Leu Gln Pro Gly Thr 500 505 510

Pro Gly Thr Gln Gly Gln Ser Pro Ser Arg Val Pro Met Leu Arg Leu 515 520 525

Ser Ser Arg Pro Glu Glu Val Thr Asp Trp Leu Gln Ala Glu Asn Phe 530 535 540

Ser Thr Ala Thr Val Arg Thr Leu Gly Ser Leu Thr Gly Ser Gln Leu 545 550 560

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Pro Arg Ile Leu Ser Arg Leu Glu Ala Val Arg Arg Met Leu Gly Ile 580 585 590

Ser Pro

<210> 41

<211> 3600

<212> DNA

<213> Homo sapiens

<400> 41

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<210> 42

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Pro His Leu His Gly Val Phe Glu Gln Val Pro Ala Pro Trp Trp Thr 40

<211> 963

<212> PRT <213> Homo sapiens

<400> 42

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Ser Leu Tyr Pro Val Ala Ser Phe Leu Ala Ala Pro Met Ser Glu Leu 65

Val Pro Asp Leu Ser Phe Gln Val Asp Leu His Thr Gly Leu Ser Glu 95

Phe Ser Val Thr Gln Arg Arg Leu Ala His Gly Trp Asn Glu Phe Val

- Ala Asp Asn Ser Glu Pro Val Trp Lys Lys Tyr Leu Asp Gln Phe Lys
 115 120 125
- Asn Pro Leu Ile Leu Leu Leu Gly Ser Ala Leu Val Ser Val Leu 130 135 140
- Thr Lys Glu Tyr Glu Asp Ala Val Ser Ile Ala Thr Ala Val Leu Val 145 150 155 160
- Val Val Thr Val Ala Phe Ile Gln Glu Tyr Arg Ser Glu Lys Ser Leu 165 170 175
- Glu Glu Leu Thr Lys Leu Val Pro Pro Glu Cys Asn Cys Leu Arg Glu 180 185 190
- Gly Lys Leu Gln His Leu Leu Ala Arg Glu Leu Val Pro Gly Asp Val 195 200 205
- Val Ser Leu Ser Ile Gly Asp Arg Ile Pro Ala Asp Ile Arg Leu Thr 210 215 220
- Glu Val Thr Asp Leu Leu Val Asp Glu Ser Ser Phe Thr Gly Glu Ala 225 230 235 240
- Glu Pro Cys Ser Lys Thr Asp Ser Pro Leu Thr Gly Gly Gly Asp Leu 245 250 255
- Thr Thr Leu Ser Asn Ile Val Phe Met Gly Thr Leu Val Gln Tyr Gly 260 265 270

Arg Gly Gln Gly Val Val Ile Gly Thr Gly Glu Ser Ser Gln Phe Gly 275 280 285

- Glu Val Phe Lys Met Met Gln Ala Glu Glu Thr Pro Lys Thr Pro Leu 290 295 300
- Gln Lys Ser Met Asp Arg Leu Gly Lys Gln Leu Thr Leu Phe Ser Phe 305 310 315 320
- Gly Ile Ile Gly Leu Ile Met Leu Ile Gly Trp Ser Gln Gly Lys Gln 325 330 335
- Leu Leu Ser Met Phe Thr Ile Gly Val Ser Leu Ala Val Ala Ala Ile 340 345 350
- Pro Glu Gly Leu Pro Ile Val Val Met Val Thr Leu Val Leu Gly Val 355 360 365
- Leu Arg Met Ala Lys Lys Arg Val Ile Val Lys Lys Leu Pro Ile Val 370 380
- Glu Thr Leu Gly Cys Cys Ser Val Leu Cys Ser Asp Lys Thr Gly Thr 385 390 395 400
- Leu Thr Ala Asn Glu Met Thr Val Thr Gln Leu Val Thr Ser Asp Gly 405 410 415
- Leu Arg Ala Glu Val Ser Gly Val Gly Tyr Asp Gly Gln Gly Thr Val 420 425 430
- Cys Leu Leu Pro Ser Lys Glu Val Ile Lys Glu Phe Ser Asn Val Ser 435 440 445
- Val Gly Lys Leu Val Glu Ala Gly Cys Val Ala Asn Asn Ala Val Ile 450 455 460
- Arg Lys Asn Ala Val Met Gly Gln Pro Thr Glu Gly Ala Leu Met Ala 465 470 475 480
- Leu Ala Met Lys Met Asp Leu Ser Asp Ile Lys Asn Ser Tyr Ile Arg 485 490 495

. . .

Lys Lys Glu Ile Pro Phe Ser Ser Glu Gln Lys Trp Met Ala Val Lys 500 505 510

- Cys Ser Leu Lys Thr Glu Asp Gln Glu Asp Ile Tyr Phe Met Lys Gly 515 520 525
- Ala Leu Glu Glu Val Ile Arg Tyr Cys Thr Met Tyr Asn Asn Gly Gly 530 535 540
- Ile Pro Leu Pro Leu Thr Pro Gln Gln Arg Ser Phe Cys Leu Gln Glu 545 550 555 560
- Glu Lys Arg Met Gly Ser Leu Gly Leu Arg Val Leu Ala Leu Ala Ser 565 570 575
- Gly Pro Glu Leu Gly Arg Leu Thr Phe Leu Gly Leu Val Gly Ile Ile 580 585 590
- Asp Pro Pro Arg Val Gly Val Lys Glu Ala Val Gln Val Leu Ser Glu 595 600 605
- Ser Gly Val Ser Val Lys Met Ile Thr Gly Asp Ala Leu Glu Thr Ala 610 615 620
- Leu Ala Ile Gly Arg Asn Ile Gly Leu Cys Asn Gly Lys Leu Gln Ala 625 630 635 640
- Met Ser Gly Glu Glu Val Asp Ser Val Glu Lys Gly Glu Leu Ala Asp 645 650 \cdot 655
- Arg Val Gly Lys Val Ser Val Phe Phe Arg Thr Ser Pro Lys His Lys 660 665 670
- Leu Lys Ile Ile Lys Ala Leu Gln Glu Ser Gly Ala Ile Val Ala Met 675 680 685
- Thr Gly Asp Gly Val Asn Asp Ala Val Ala Leu Lys Ser Ala Asp Ile 690 695 700
- Gly Ile Ala Met Gly Gln Thr Gly Thr Asp Val Ser Lys Glu Ala Ala 705 710 715 720

Asn Met Ile Leu Val Asp Asp Asp Phe Ser Ala Ile Met Asn Ala Val 725 730 735

- Glu Glu Gly Lys Gly Ile Phe Tyr Asn Ile Lys Asn Phe Val Arg Phe 740 745 750
- Gln Leu Ser Thr Ser Ile Ser Ala Leu Ser Leu Ile Thr Leu Ser Thr 755 760 765
- Val Phe Asn Leu Pro Ser Pro Leu Asn Ala Met Gln Ile Leu Trp Ile 770 775 780
- Asn Ile Ile Met Asp Gly Pro Pro Ala Gln Ser Leu Gly Val Glu Pro 785 790 795 800
- Val Asp Lys Asp Ala Phe Arg Gln Pro Pro Arg Ser Val Arg Asp Thr 805 810 815
- Ile Leu Ser Arg Ala Leu Ile Leu Lys Ile Leu Met Ser Ala Ala Ile 820 825 830
- Ile Ile Ser Gly Thr Leu Phe Ile Phe Trp Lys Glu Met Pro Glu Asp 835 840 845
- Arg Ala Ser Thr Pro Arg Thr Thr Met Thr Phe Thr Cys Phe Val 850 860
- Phe Phe Asp Leu Phe Asn Ala Leu Thr Cys Arg Ser Gln Thr Lys Leu 865 870 875 880
- Ile Phe Glu Ile Gly Phe Leu Arg Asn His Met Phe Leu Tyr Ser Val 885 890 895
- Leu Gly Ser Ile Leu Gly Gln Leu Ala Val Ile Tyr Ile Pro Pro Leu 900 905 910
- Gln Arg Val Phe Gln Thr Glu Asn Leu Gly Ala Leu Asp Leu Leu Phe 915 920 925
- Leu Thr Gly Leu Ala Ser Ser Val Phe Ile Leu Ser Glu Leu Leu Lys 930 935 940

Leu Cys Glu Lys Tyr Cys Cys Ser Pro Lys Arg Val Gln Met His Pro 945 950 955 960

Glu Asp Val

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<213> Homo sapiens

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<210> 44

<211> 509

<212> PRT

<213> Homo sapiens

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Ser Leu Leu Lys Asp Glu Ala Leu Ala Ile Ala Ala Leu Glu Leu Leu 35 40 45

Pro Arg Glu Leu Phe Pro Pro Leu Phe Met Ala Ala Phe Asp Gly Arg 50 55 60

His Ser Gln Thr Leu Lys Ala Met Val Gln Ala Trp Pro Phe Thr Cys 75 80

Leu Pro Leu Gly Val Leu Met Lys Gly Gln His Leu His Leu Glu Thr Phe Lys Ala Val Leu Asp Gly Leu Asp Val Leu Leu Ala Gln Glu Val Arg Pro Arg Arg Trp Lys Leu Gln Val Leu Asp Leu Arg Lys Asn Ser 120 His Gln Asp Phe Trp Thr Val Trp Ser Gly Asn Arg Ala Ser Leu Tyr 135 Ser Phe Pro Glu Pro Glu Ala Ala Gln Pro Met Thr Lys Lys Arg Lys Val Asp Gly Leu Ser Thr Glu Ala Glu Gln Pro Phe Ile Pro Val Glu 170 Val Leu Val Asp Leu Phe Leu Lys Glu Gly Ala Cys Asp Glu Leu Phe 180 Ser Tyr Leu Ile Glu Lys Val Lys Arg Lys Asn Val Leu Arg Leu Cys Cys Lys Leu Lys Ile Phe Ala Met Pro Met Gln Asp Ile Lys 215 Met Ile Leu Lys Met Val Gln Leu Asp Ser Ile Glu Asp Leu Glu Val 225 Thr Cys Thr Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu Gly Gln Met Ile Asn Leu Arg Arg Leu Leu Ser His Ile His Ala 260 265 Ser Ser Tyr Ile Ser Pro Glu Lys Glu Glu Gln Tyr Ile Ala Gln Phe Thr Ser Gln Phe Leu Ser Leu Gln Cys Leu Gln Ala Leu Tyr Val Asp

295

Ser Leu Phe Phe Leu Arg Gly Arg Leu Asp Gln Leu Leu Arg His Val 310 315 Met Asn Pro Leu Glu Thr Leu Ser Ile Thr Asn Cys Arg Leu Ser Glu 330 Gly Asp Val Met His Leu Ser Gln Ser Pro Ser Val Ser Gln Leu Ser 345 340 Val Leu Ser Leu Ser Gly Val Met Leu Thr Asp Val Ser Pro Glu Pro 360 355 Leu Gln Ala Leu Leu Glu Arg Ala Ser Ala Thr Leu Gln Asp Leu Val 370 Phe Asp Glu Cys Gly Ile Thr Asp Asp Gln Leu Leu Ala Leu Leu Pro Ser Leu Ser His Cys Ser Gln Leu Thr Thr Leu Ser Phe Tyr Gly Asn 405 410 Ser Ile Ser Ile Ser Ala Leu Gln Ser Leu Leu Gln His Leu Ile Gly Leu Ser Asn Leu Thr His Val Leu Tyr Pro Val Pro Leu Glu Ser Tyr 435 440 Glu Asp Ile His Gly Thr Leu His Leu Glu Arg Leu Ala Tyr Leu His 450 455 Ala Arg Leu Arg Glu Leu Leu Cys Glu Leu Gly Arg Pro Ser Met Val Trp Leu Ser Ala Asn Pro Cys Pro His Cys Gly Asp Arg Thr Phe Tyr 490 Asp Pro Glu Pro Ile Leu Cys Pro Cys Phe Met Pro Asn 500 · 505 <210> 45

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<212> DNA

1445

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<210> 46 <211> 297 <212> PRT <213> Homo sapiens

<400> 46

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Gln Glu Leu Met Ser Met Lys Glu Val Gly Asp Gly Leu Gln Asp Gln 20 25 30

Gln Thr Ala Leu Glu Gln Leu Glu Ile Ser Gly Gly Pro Val Pro 50 60

Gly Ser Pro Glu Gly Pro Arg Thr Gln Cys Glu His Pro Cys Trp Glu 65 70 75 80

Gly Gly Arg Gly Pro Ala Arg Pro Thr Val Cys Ser Pro Ser Ser Gln 85 90 95

Pro Ser Leu Gly Ser Ser Thr Lys Phe Pro Ser His Arg Ser Val Cys 100 105 110

Gly Arg Asp Leu Ala Pro Leu Pro Arg Thr Gln Pro His Gln Ser Cys 115 120 125

Ala Gln Gln Gly Pro Glu Arg Val Glu Pro Asp Asp Trp Thr Ser Thr 130 135 140

Leu Met Ser Arg Gly Arg Asn Arg Gln Pro Leu Val Leu Gly Asp Asn 145 150 155 160

Val Phe Ala Asp Leu Val Gly Asn Trp Leu Asp Leu Pro Glu Leu Glu 165 170 175

Lys Gly Glu Lys Gly Glu Thr Gly Gly Ala Arg Glu Pro Lys Gly 180 185 190

Glu Lys Gly Gln Pro Gln Glu Leu Gly Arg Arg Phe Ala Leu Thr Ala 195 200 205

Asn Ile Phe Lys Lys Phe Leu Arg Ser Val Arg Pro Asp Arg Asp Arg 210 215 220

86

Leu Leu Lys Glu Lys Pro Gly Trp Val Thr Pro Met Val Pro Glu Ser 225 230 235 240

Arg Thr Gly Arg Ser Gln Lys Val Lys Lys Arg Ser Leu Ser Lys Gly 245 250 255

Ser Gly His Phe Pro Phe Pro Gly Thr Gly Glu His Arg Arg Gly Glu 260 265 270

Asn Pro Pro Thr Ser Cys Pro Lys Ala Leu Glu His Ser Pro Ser Gly 275 280 285

Phe Asp Ile Asn Thr Ala Val Trp Val 290 295

<210> 47

<211> 1919

<212> DNA

<213> Homo sapiens

<400> 47

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<400> 48

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Gly Ala Glu Gly Leu His Cys Ser Glu His Leu Leu Glu Lys Ala

Pro Ser Tyr Gly Ser Glu Gly Pro Ala Gln Arg Val Leu Glu Gly Thr

Leu Leu Glu Phe Thr Lys Asp Met Asp Gln Leu Leu Gln Leu Thr Arg 55

<210> 48 <211> 308 <212> PRT

<213> Homo sapiens

Lys Leu Glu Ser Ser Gln Pro Arg Gln Gly Glu Gly Asn Arg Thr Pro 65 70 75 80

- Glu Ser Gln Lys Arg Lys Ser Lys Lys Ala Thr Lys Gln Thr Leu Gln 85 90 95
- Asp Ser Phe Leu Leu Asp Leu Lys Ser Pro Pro Ser Phe Pro Val Glu
 100 105 110
- Ile Ser Asp Arg Leu Pro Ala Ala Ser Trp Glu Gly Gln Glu Ser Cys 115 120 125
- Trp Asn Lys Gln Thr Ser Lys Ser Glu Gly Thr Gln Pro Glu Gly Thr 130 135 140
- Tyr Gly Glu Gln Leu Val Pro Glu Leu Cys Asn Gln Ser Glu Ser Ser 145 150 155 160
- Gly Glu Asp Phe Phe Leu Lys Ser Arg Leu Gln Glu Gln Asp Val Trp 165 170 175
- Arg Arg Ser Thr Ser Phe Tyr Thr His Met Cys Asn Pro Trp Val Ser 180 185 190
- Leu Leu Gly Ala Val Gly Ser Leu Leu Ile Met Phe Val Ile Gln Trp 195 200 205
- Val Tyr Thr Leu Val Asn Met Gly Val Ala Ala Ile Val Tyr Phe Tyr 210 215 220
- Ile Gly Arg Ala Ser Pro Gly Leu His Leu Gly Ser Ala Ser Asn Phe 225 230 235 240
- Ser Phe Phe Arg Trp Met Arg Ser Leu Leu Leu Pro Ser Cys Arg Ser 245 250 255
- Leu Gln Ser Pro Gln Glu Gln Ile Ile Leu Ala Pro Ser Leu Ala Lys 260 265 270
- Val Asp Met Glu Met Thr Gln Leu Thr Gln Glu Asn Ala Asp Phe Ala 275 280 285

Thr Arg Asp Arg Tyr His His Ser Ser Leu Val Asn Arg Glu Gln Leu 290 295 300

Met Pro His Tyr 305

<210> 49 <211> 772 <212> DNA

<213> Homo sapiens

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<210> 50

<211> 115

<212> PRT

<213> Homo sapiens

<400> 50

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Ile Cys Phe Leu Thr Lys Ser Asp Gly Lys Ser Val Lys Lys Arg Ser 20 25 30

90

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Val Ser Glu Ile Gln Leu Met His Asn Leu Gly Lys His Leu Asn Ser

Met Glu Arg Val Glu Trp Leu Arg Lys Leu Gln Asp Val His Asn 55

Phe Val Ala Leu Gly Ala Pro Leu Ala Pro Arg Asp Ala Gly Ser Gln 70

Arg Pro Arg Lys Lys Glu Asp Asn Val Leu Val Glu Ser His Glu Lys 85

Ser Leu Gly Glu Ala Asp Lys Ala Asp Val Asn Val Leu Thr Lys Ala 105

Lys Ser Gln 115

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<213> Homo sapiens

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120

180

600

780

360 cacaggetec tactactgag gageaggagg etgetgtete etecteetet eetetggtee 420

480 qagcctctqc cttacccact accatcagct tcacttgctg gaggcaaccc aatgagggtt

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<210> 52 <211> 317

<212> PRT

<213> Homo sapiens

<400> 52

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Glu Ala Glu Glu Glu Ala Leu Gly Leu Val Gly Ala Gln Ala Pro Thr 20 25 30

Thr Glu Glu Glu Ala Ala Val Ser Ser Ser Pro Leu Val Pro 35 40 45

Gly Thr Leu Glu Glu Val Pro Ala Ala Glu Ser Ala Gly Pro Pro Gln 50 55 60

Ser Pro Gln Gly Ala Ser Ala Leu Pro Thr Thr Ile Ser Phe Thr Cys 70 75 80

Trp Arg Gln Pro Asn Glu Gly Ser Ser Ser Gln Glu Glu Gly Pro 85 90 95

Ser Thr Ser Pro Asp Ala Glu Ser Leu Phe Arg Glu Ala Leu Ser Asn 100 105 110

Lys Val Asp Glu Leu Ala His Phe Leu Leu Arg Lys Tyr Arg Ala Lys 115 120 125

Glu Leu Val Thr Lys Ala Glu Met Leu Glu Arg Val Ile Lys Asn Tyr 130 135 140

Lys Arg Cys Phe Pro Val Ile Phe Gly Lys Ala Ser Glu Ser Leu Lys 145 150 155 160

Met Ile Phe Gly Ile Asp Val Lys Glu Val Asp Pro Thr Ser Asn Thr 165 170 175

Tyr Thr Leu Val Thr Cys Leu Gly Leu Ser Tyr Asp Gly Leu Leu Gly 180 185 190

Asn Asn Gln Ile Phe Pro Lys Thr Gly Leu Leu Ile Ile Val Leu Gly 195 200 205

Thr Ile Ala Met Glu Gly Asp Ser Ala Ser Glu Glu Glu Ile Trp Glu 210 215 220

Glu Leu Gly Val Met Gly Val Tyr Asp Gly Arg Glu His Thr Val Tyr 225 230 235 240

Gly Glu Pro Arg Lys Leu Leu Thr Gln Asp Trp Val Gln Glu Asn Tyr 245 250 255

Leu Glu Tyr Arg Gln Val Pro Gly Ser Asn Pro Ala Arg Tyr Glu Phe 260 265 270

Leu Trp Gly Pro Arg Ala Leu Ala Glu Thr Ser Tyr Val Lys Val Leu 275 280 285

Glu His Val Val Arg Val Asn Ala Arg Val Arg Ile Ala Tyr Pro Ser 290 295 300

Leu Arg Glu Ala Ala Leu Leu Glu Glu Glu Gly Val 305 310 315

<210> 53

<211> 1833

<212> DNA

<213> Homo sapiens

<400> 53

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<210> 54

<211> 315

<212> PRT

<213> Homo sapiens

<400> 54

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Glu Ala Gln Gly Glu Asp Leu Gly Leu Met Gly Ala Gln Glu Pro Thr $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$

Gly Glu Glu Glu Glu Thr Thr Ser Ser Ser Asp Ser Lys Glu Glu Glu 35 40

Val Ser Ala Ala Gly Ser Ser Ser Pro Pro Gln Ser Pro Gln Gly Gly 50 55 60

Ala Ser Ser Ser Ile Ser Val Tyr Tyr Thr Leu Trp Ser Gln Phe Asp 65 70 75 80

Glu Gly Ser Ser Ser Gln Glu Glu Glu Glu Pro Ser Ser Val Asp 85 90 95

Pro Ala Gln Leu Glu Phe Met Phe Gln Glu Ala Leu Lys Leu Lys Val 100 105 110

Ala Glu Leu Val His Phe Leu Leu His Lys Tyr Arg Val Lys Glu Pro 115 120 125

Val Thr Lys Ala Glu Met Leu Glu Ser Val Ile Lys Asn Tyr Lys Arg 130 135 140

Tyr Phe Pro Val Ile Phe Gly Lys Ala Ser Glu Phe Met Gln Val Ile 145 150 155 160

Phe Gly Thr Asp Val Lys Glu Val Asp Pro Ala Gly His Ser Tyr Ile 165 170 175

Leu Val Thr Ala Leu Gly Leu Ser Cys Asp Ser Met Leu Gly Asp Gly 180 185 190

His Ser Met Pro Lys Ala Ala Leu Leu Ile Ile Val Leu Gly Val Ile 195 200 205.

Leu Thr Lys Asp Asn Cys Ala Pro Glu Glu Val Ile Trp Glu Ala Leu 210 215 220

Ser Val Met Gly Val Tyr Val Gly Lys Glu His Met Phe Tyr Gly Glu 225 230 235 240

Pro Arg Lys Leu Leu Thr Gln Asp Trp Val Gln Glu Asn Tyr Leu Glu 245 250 255

Tyr Arg Gln Val Pro Gly Ser Asp Pro Ala His Tyr Glu Phe Leu Trp 260 265 270

Gly Ser Lys Ala His Ala Glu Thr Ser Tyr Glu Lys Val Ile Asn Tyr 275 280 285

Leu Val Met Leu Asn Ala Arg Glu Pro Ile Cys Tyr Pro Ser Leu Tyr 290 295 300

Glu Glu Val Leu Gly Glu Glu Gln Glu Gly Val 305 310 315

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<211> 503

<212> DNA

<213> Homo sapiens

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<210> 56

<211> 93

<212> PRT

<213> Homo sapiens

<400> 56

Met Lys Leu Leu Met Val Leu Met Leu Ala Ala Leu Ser Gln His Cys 1 5 10 15

Tyr Ala Gly Ser Gly Cys Pro Leu Leu Glu Asn Val Ile Ser Lys Thr 20 25 30

Ile Asn Pro Gln Val Ser Lys Thr Glu Tyr Lys Glu Leu Leu Gln Glu 35 40 45

Phe Ile Asp Asp Asn Ala Thr Thr Asn Ala Ile Asp Glu Leu Lys Glu 50 55 60

Cys Phe Leu Asn Gln Thr Asp Glu Thr Leu Ser Asn Val Glu Val Phe 65 70 75 80

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<212> DNA

<213> Homo sapiens

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caggaagtgt g						180
aaaaatgtgt g	jctatgacca	ctttttcccg	gtgtcccaca	tccggctgtg	ggccctccag	240
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<210> 58

<211> 261

<212> PRT

<213> Homo sapiens

<400> 58

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Ser Thr Ser Ile Gly Lys Val Trp Ile Thr Val Ile Phe Ile Phe Arg 20 25 30

Val Met Ile Leu Val Val Ala Ala Gl
n Glu Val Trp Gly Asp Glu Gl
n 35 40 45

Glu Asp Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Lys Asn Val Cys 50 60

Tyr Asp His Phe Phe Pro Val Ser His Ile Arg Leu Trp Ala Leu Gln 65 70 75 80

Leu Ile Phe Val Ser Thr Pro Ala Leu Leu Val Ala Met His Val Ala 85 90 95

Tyr Tyr Arg His Glu Thr Thr Arg Lys Phe Arg Arg Gly Glu Lys Arg 100 105 110

Asn Asp Phe Lys Asp Ile Glu Asp Ile Lys Lys His Lys Val Arg Ile 115 120 125

Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser Ser Ile Phe Phe Arg Ile 130 135 140

Ile Phe Glu Ala Ala Phe Met Tyr Val Phe Tyr Phe Leu Tyr Asn Gly 145 150 155 160

Tyr His Leu Pro Trp Val Leu Lys Cys Gly Ile Asp Pro Cys Pro Asn 165 170 175

Leu Val Asp Cys Phe Ile Ser Arg Pro Thr Glu Lys Thr Val Phe Thr 180 185 190

Ile Phe Met Ile Ser Ala Ser Val Ile Cys Met Leu Leu Asn Val Ala 195 200 205

Glu Leu Cys Tyr Leu Leu Leu Lys Val Cys Phe Arg Arg Ser Lys Arg 210 $$ 215 $$ 220

Ala Gln Thr Gln Lys Asn His Pro Asn His Ala Leu Lys Glu Ser Lys 225 230 235 240

Gln Asn Glu Met Asn Glu Leu Ile Ser Asp Ser Gly Gln Asn Ala Ile 245 250 255

Thr Gly Phe Pro Ser 260

<210> 59

<211> 1064

<212> DNA

<213> Homo sapiens

<400> 59

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<210> 60

<211> 112

<212> PRT

<213> Homo sapiens

<400> 60

Met Val Ser Ala Gly Val Ser Ile Pro Thr Pro Pro Ile Lys Phe Val 1 5 10 15

Ile Ser Pro Lys Phe Ser Thr Arg Gly Ser Ala Pro Pro Trp Ala Pro
20 . 25 30

Pro Pro Ala Thr Asn Gly Thr Pro Pro Pro Leu Leu Ser Leu Ile Pro 35 40 45

Pro Pro Phe Pro Pro Ser Ser Ser Pro Pro Pro Phe Pro Pro Val Ser 50 55 60

Ile Ser Arg Leu Thr Pro Leu Ser Pro Tyr Ser Thr Asn His Pro Pro 65 70 75 80

Leu Pro Pro Leu Tyr Arg Pro Pro Pro Pro Ile Tyr Ile Asn Pro Thr 85 90 95

Ala Ser Leu Ser Phe Pro Pro Leu Phe Ser Pro Thr Pro Ser Tyr Pro 100 105 110

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<212> DNA

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<210> 62 <211> 684 <212> PRT <213> Homo sapiens

<400> 62

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- Asp Gly Glu Ala Gly Pro Pro Gly Leu Pro Gly Pro Pro Gly Pro Lys 50 55 60
- Gly Ala Pro Gly Lys Pro Gly Lys Pro Gly Glu Ala Gly Leu Pro Gly 65 70 75 80
- Leu Pro Gly Val Asp Gly Leu Thr Gly Arg Asp Gly Pro Pro Gly Pro 85 90 95
- Lys Gly Ala Pro Gly Glu Arg Gly Ser Leu Gly Pro Pro Gly Pro Pro 100 105 110
- Gly Leu Gly Gly Lys Gly Leu Pro Gly Pro Pro Gly Glu Ala Gly Val 115 120 125
- Ser Gly Pro Pro Gly Gly Ile Gly Leu Arg Gly Pro Pro Gly Pro Pro 130 135 140
- Gly Leu Pro Gly Leu Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly 145 150 155 160
- His Pro Gly Val Leu Pro Glu Gly Ala Thr Asp Leu Gln Cys Pro Ser 165 170 175
- Ile Cys Pro Pro Gly Pro Pro Gly Pro Pro Gly Met Pro Gly Phe Lys
 180 185 190
- Gly Pro Thr Gly Tyr Lys Gly Glu Gln Gly Glu Val Gly Lys Asp Gly 195 200 205
- Glu Lys Gly Asp Pro Gly Pro Pro Gly Pro Ala Gly Leu Pro Gly Ser 210 215 220
- Val Gly Leu Gln Gly Pro Arg Gly Leu Arg Gly Leu Pro Gly Pro Leu 225 230 235 240

Gly Pro Pro Gly Asp Arg Gly Pro Ile Gly Phe Arg Gly Pro Pro Gly 245 250 255

- Glu Gly Phe Arg Gly Pro Lys Gly Asp Leu Gly Arg Pro Gly Pro Lys 275 280 285
- Gly Thr Pro Gly Val Ala Gly Pro Ser Gly Glu Pro Gly Met Pro Gly 290 295 300
- Lys Asp Gly Gln Asn Gly Val Pro Gly Leu Asp Gly Gln Lys Gly Glu 305 310 315 320
- Ala Gly Arg Asn Gly Ala Pro Gly Glu Lys Gly Pro Asn Gly Leu Pro 325 330 335
- Gly Leu Pro Gly Arg Ala Gly Ser Lys Gly Glu Lys Gly Glu Arg Gly 340 345 350
- Arg Ala Gly Glu Leu Gly Glu Ala Gly Pro Ser Gly Glu Pro Gly Val 355 360 365
- Pro Gly Asp Ala Gly Met Pro Gly Glu Arg Gly Glu Ala Gly His Arg 370 375 380
- Gly Ser Ala Gly Ala Leu Gly Pro Gln Gly Pro Pro Gly Ala Pro Gly 385 390 395 400
- Val Arg Gly Phe Gln Gly Gln Lys Gly Ser Met Gly Asp Pro Gly Leu 405 410 415
- Pro Gly Pro Gln Gly Leu Arg Gly Asp Val Gly Asp Arg Gly Pro Gly 420 425 430
- Gly Ala Ala Gly Pro Lys Gly Asp Gln Gly Ile Ala Gly Ser Asp Gly 435 440 445
- Leu Pro Gly Asp Lys Gly Glu Leu Gly Pro Ser Gly Leu Val Gly Pro 450 460

Lys Gly Glu Ser Gly Ser Arg Gly Glu Leu Gly Pro Lys Gly Thr Gln 465 470 475 480

- Gly Pro Asn Gly Thr Ser Gly Val Gln Gly Val Pro Gly Pro Pro Gly 485 490 495
- Pro Leu Gly Leu Gln Gly Val Pro Gly Val Pro Gly Ile Thr Gly Lys 500 505 510
- Pro Gly Val Pro Gly Lys Glu Ala Ser Glu Gln Arg Ile Arg Glu Leu 515 520 525
- Cys Gly Gly Met Ile Ser Glu Gln Ile Ala Gln Leu Ala Ala His Leu 530 535 540
- Arg Lys Pro Leu Ala Pro Gly Ser Ile Gly Arg Pro Gly Pro Ala Gly 545 550 555 560
- Pro Pro Gly Pro Pro Gly Pro Pro Gly Ser Ile Gly His Pro Gly Ala 565 570 575
- Arg Gly Pro Pro Gly Tyr Arg Gly Pro Thr Gly Glu Leu Gly Asp Pro 580 585 590
- Gly Pro Arg Gly Asn Gln Gly Asp Arg Gly Asp Lys Gly Ala Ala Gly 595 600 605
- Ala Gly Leu Asp Gly Pro Glu Gly Asp Gln Gly Pro Gln Gly Pro Gln 610 615 620
- Gly Val Pro Gly Thr Ser Lys Asp Gly Gln Asp Gly Ala Pro Gly Glu 625 630 635 640
- Pro Gly Pro Pro Gly Asp Pro Gly Leu Pro Gly Ala Ile Gly Ala Gln 645 650
- Gly Thr Pro Gly Ile Cys Asp Thr Ser Ala Cys Gln Gly Ala Val Leu 660 665 670
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<213> Homo sapiens

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<210> 64

<211> 465

<212> PRT

<213> Homo sapiens

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Leu Glu Phe Glu Asn Val Gln Val Leu Thr Met Gly Asn Asp Thr Ser 20 25 30

Pro Ser Glu Gly Thr Asn Leu Asn Ala Pro Asn Ser Leu Gly Val Ser 35 40 45

Ala Leu Cys Ala Ile Cys Gly Asp Arg Ala Thr Gly Lys His Tyr Gly 50 55 60

Ala Ser Ser Cys Asp Gly Cys Lys Gly Phe Phe Arg Arg Ser Val Arg 65 70 75 80

Lys Asn His Met Tyr Ser Cys Arg Phe Ser Arg Gln Cys Val Val Asp $85 \hspace{1cm} 90 \hspace{1cm} 95$

Lys Asp Lys Arg Asn Gln Cys Arg Tyr Cys Arg Leu Lys Lys Cys Phe 100 105 110

Arg Ala Gly Met Lys Lys Glu Ala Val Gln Asn Glu Arg Asp Arg Ile 115 120 125

Ser Thr Arg Arg Ser Ser Tyr Glu Asp Ser Ser Leu Pro Ser Ile Asn 130 135 140

Ala Leu Leu Gln Ala Glu Val Leu Ser Arg Gln Ile Thr Ser Pro Val 145 150 155 160

Ser Gly Ile Asn Gly Asp Ile Arg Ala Lys Lys Ile Ala Ser Ile Ala 165 170 175

Asp Val Cys Glu Ser Met Lys Glu Gln Leu Leu Val Leu Val Glu Trp 180 185 190

Ala Lys Tyr Ile Pro Ala Phe Cys Glu Leu Pro Leu Asp Asp Gln Val

195 200 205

Ala Leu Leu Arg Ala His Ala Gly Glu His Leu Leu Gly Ala Thr 210 215 220

Lys Arg Ser Met Val Phe Lys Asp Val Leu Leu Gly Asn Asp Tyr 225 230 235 240

Ile Val Pro Arg His Cys Pro Glu Leu Ala Glu Met Ser Arg Val Ser 245 250 255

Ile Arg Ile Leu Asp Glu Leu Val Leu Pro Phe Gln Glu Leu Gln Ile 260 265 270

Asp Asp Asn Glu Tyr Ala Tyr Leu Lys Ala Ile Ile Phe Phe Asp Pro 275 280 285

Asp Ala Lys Gly Leu Ser Asp Pro Gly Lys Ile Lys Arg Leu Arg Ser 290 295 300

Gln Val Gln Val Ser Leu Glu Asp Tyr Ile Asn Asp Arg Gln Tyr Asp 305 310 315 320

Ser Arg Gly Arg Phe Gly Glu Leu Leu Leu Leu Pro Thr Leu Gln 325 330 335

Ser Ile Thr Trp Gln Met Ile Glu Gln Ile Gln Phe Ile Lys Leu Phe 340 345 350

Gly Met Ala Lys Ile Asp Asn Leu Leu Gln Glu Met Leu Leu Gly Gly 355 360 365

Ser Pro Ser Asp Ala Pro His Ala His His Pro Leu His Pro His Leu 370 375 380

Met Gln Glu His Met Gly Thr Asn Val Ile Val Ala Asn Thr Met Pro 385 390 395 400

Thr His Leu Ser Asn Gly Gln Met Cys Glu Trp Pro Arg Pro Arg Gly 405 410 415

Gln Ala Ala Thr Pro Glu Thr Pro Gln Pro Ser Pro Pro Gly Ala Ser

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Gly Ser Glu Pro Tyr Lys Leu Leu Pro Gly Ala Val Ala Thr Ile Val 435 440 445

Lys Pro Leu Ser Ala Ile Pro Gln Pro Thr Ile Thr Lys Gln Glu Val 450 455 460

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<210> 66

<211> 440

<212> PRT

<213> Homo sapiens

<400> 66

Met Glu Gln Thr Tyr Gly Glu Val Asn Gln Leu Gly Gly Val Phe Val $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Asn Gly Arg Pro Leu Pro Asn Ala Ile Arg Leu Arg Ile Val Glu Leu 20 25 30

Ala Gln Leu Gly Ile Arg Pro Cys Asp Ile Ser Arg Gln Leu Arg Val 35 40 45

Ser His Gly Cys Val Ser Lys Ile Leu Ala Arg Tyr Asn Glu Thr Gly 50 60

Ser Ile Leu Pro Gly Ala Ile Gly Gly Ser Lys Pro Arg Val Thr Thr 65 70 75 80

Pro Asn Val Val Lys His Ile Arg Asp Tyr Lys Gln Gly Asp Pro Gly 85 90 95

Ile Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu Ala Asp Gly Val Cys
100 105 110

Asp Lys Tyr Asn Val Pro Ser Val Ser Ser Ile Ser Arg Ile Leu Arg 115 120 125

Asn Lys Ile Gly Ser Leu Ala Gln Pro Gly Pro Tyr Glu Ala Ser Lys 130 140

Gln Pro Pro Ser Gln Pro Thr Leu Pro Tyr Asn His Ile Tyr Gln Tyr 145 150 155 160

Pro Tyr Pro Ser Pro Val Ser Pro Thr Gly Ala Lys Met Gly Ser His $165 \\ 170 \\ 175 \\$

- Pro Gly Val Pro Gly Thr Ala Gly His Val Ser Ile Pro Arg Ser Trp 180 185 190
- Pro Ser Ala His Ser Val Ser Asn Ile Leu Gly Ile Arg Thr Phe Met 195 200 205
- Glu Gln Thr Gly Ala Leu Ala Gly Ser Glu Gly Thr Ala Tyr Ser Pro 210 215 220
- Lys Met Glu Asp Trp Ala Gly Val Asn Arg Thr Ala Phe Pro Ala Thr 225 230 235 240
- Pro Ala Val Asn Gly Leu Glu Lys Pro Ala Leu Glu Ala Asp Ile Lys 245 250 255
- Tyr Thr Gln Ser Ala Ser Thr Leu Ser Ala Val Gly Gly Phe Leu Pro 260 265 270
- Gly Gly Tyr Leu Ala Pro Gly Pro Pro Trp Pro Pro Ala Gln Gly 290 295 300
- Pro Pro Leu Ala Pro Pro Gly Ala Gly Val Ala Val His Gly Gly Glu 305 310 315 320
- Leu Ala Ala Met Thr Phe Lys His Pro Ser Arg Glu Gly Ser Leu 325 330 335
- Pro Ala Pro Ala Ala Arg Pro Arg Thr Pro Ser Val Ala Tyr Thr Asp 340 345 350
- Cys Pro Ser Arg Pro Arg Pro Pro Arg Gly Ser Ser Pro Arg Thr Arg 355 360 365
- Ala Arg Arg Glu Arg Gln Ala Asp Pro Gly Ala Gln Val Cys Ala Ala 370 375 380

Ala Pro Ala Ile Gly Thr Gly Arg Ile Gly Gly Leu Ala Glu Glu Glu Ala Ser Ala Gly Pro Arg Gly Ala Arg Pro Ala Ser Pro Gln Ala Gln 410 Pro Cys Leu Trp Pro Asp Pro Pro His Phe Leu Tyr Trp Ser Gly Phe 425 Leu Gly Phe Ser Glu Leu Gly Phe 435 <210> 67 <211> 416 <212> DNA <213> Homo sapiens <400> 67 ttatcttaag agtctttatt taacacatat agtacacatt ttcagtcatt tcatcatcat 60 ccaagtacat taagatacat acccatgtat attacaaggc ttattgttca ctcatcatct 120 180 tccctttcta ctttaccttc tcatttcttg aagtctctat tctcattaat ttgttattta 240 qttacaqtcc tcttttcaqt ttcttcagat ggggatatgc agatgataga ttcttggaat 300 cctttctgca tccctttcac tctggcaggt gaatgatgct tggctggaaa gagacttctt ggttactttc cttttctctt aacaggtata gatatgattc cactgtctga taccagtcca 360 attetttee cattgeaaat aacttette tgtetggaat ettatatat tttete 416 <210> 68 <211> 108 <212> PRT <213> Homo sapiens <400> 68

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Leu Pro Ser His Phe Leu Lys Ser Leu Phe Ser Leu Ile Cys Tyr Leu 20 25 30

Val Thr Val Leu Phe Ser Val Ser Ser Asp Gly Asp Met Gln Met Ile 35 40 45

Asp Ser Trp Asn Pro Phe Cys Ile Pro Phe Thr Leu Ala Gly Glu Leu 50 55 60

Ala Gly Lys Arg Leu Leu Gly Tyr Phe Pro Phe Leu Leu Thr Gly Ile 65 70 75 80

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<211> 2595

<212> DNA

<213> Homo sapiens

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<210> 70

<211> 330

<212> PRT

<213> Homo sapiens

<400> 70

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Thr Cys Ser Ala Arg Ala Tyr Pro Ser Asp His Arg Ile Thr Thr Phe 20 25 30

Gln Ser Cys Ala Val Ser Ala Asn Ser Cys Gly Gly Asp Asp Arg Phe 35 40 45

Leu Val Gly Arg Gly Val Gln Ile Gly Ser Pro His His His His 50 55 60

His His His His Pro Gln Pro Ala Thr Tyr Gln Thr Ser Gly Asn 65 70 75 80

Leu Gly Val Ser Tyr Ser His Ser Ser Cys Gly Pro Ser Tyr Gly Ser 85 90 95

Gln Asn Phe Ser Ala Pro Tyr Ser Pro Tyr Ala Leu Asn Gln Glu Ala 100 105 110

Asp Val Ser Gly Gly Tyr Pro Gln Cys Ala Pro Ala Val Tyr Ser Gly 115 120 125

Asn Leu Ser Ser Pro Met Val Gln His His His His Gln Gly Tyr 130 135 140

Ala Gly Gly Ala Val Gly Ser Pro Gln Tyr Ile His His Ser Tyr Gly 145 150 155 160

Gln Glu His Gln Ser Leu Ala Leu Ala Thr Tyr Asn Asn Ser Leu Ser 165 170 175

Pro Leu His Ala Ser His Gln Glu Ala Cys Arg Ser Pro Ala Ser Glu 180 185 190

Thr Ser Ser Pro Ala Gln Thr Phe Asp Trp Met Lys Val Lys Arg Asn 195 200 205

Pro Pro Lys Thr Gly Lys Val Gly Glu Tyr Gly Tyr Leu Gly Gln Pro 210 215 220

Asn Ala Val Arg Thr Asn Phe Thr Thr Lys Gln Leu Thr Glu Leu Glu 225 230 235 240

Lys Glu Phe His Phe Asn Lys Tyr Leu Thr Arg Ala Arg Arg Val Glu 245 250 255

Ile Ala Ala Ser Leu Gln Leu Asn Glu Thr Gln Val Lys Ile Trp Phe $260 \hspace{1cm} 265 \hspace{1cm} , \hspace{1cm} 270 \hspace{1cm}$

Gln Asn Arg Arg Met Lys Gln Lys Lys Arg Glu Lys Glu Gly Leu Leu 275 280 285

Pro Ile Ser Pro Ala Thr Pro Pro Gly Asn Asp Glu Lys Ala Glu Glu 290 295 300

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Ser Thr Ser Asp Thr Leu Thr Thr Ser His 325 330

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<211> 222

<212> PRT

<213> Homo sapiens

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Gln Ser Cys Ala Val Ser Ala Asn Ser Cys Gly Gly Asp Asp Arg Phe 35 40 45

Leu Val Gly Arg Gly Val Gln Ile Gly Ser Pro His His His His 50 55 60

His His His His Pro Gln Pro Ala Thr Tyr Gln Thr Ser Gly Asn 65 70 75 80

Leu Gly Val Ser Tyr Ser His Ser Ser Cys Gly Pro Ser Tyr Gly Ser 85 90 95

Gln Asn Phe Ser Ala Pro Tyr Ser Pro Tyr Ala Leu Asn Gln Glu Ala 100 105 110

Asp Val Ser Gly Gly Tyr Pro Gln Cys Ala Pro Ala Val Tyr Ser Gly 115 120 125

Asn Leu Ser Ser Pro Met Val Gln His His His His Gln Gly Tyr 130 140

Ala Gly Gly Ala Val Gly Ser Pro Gln Tyr Ile His His Ser Tyr Gly 150 150 155 160

Gln Glu His Gln Ser Leu Ala Leu Ala Thr Tyr Asn Asn Ser Leu Ser 165 170 175

Pro Leu His Ala Ser His Gln Glu Ala Cys Arg Ser Pro Ala Ser Glu 180 185 190

Thr Ser Ser Pro Ala Gln Thr Phe Asp Trp Met Lys Val Lys Arg Asn 195 200 205

Pro Pro Lys Thr Gly Gln Ser Cys Trp Leu Val Asp Ala Pro 210 215 220

<210> 72

<211> 132

<212> PRT

<213> Homo sapiens

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Thr Cys Ser Ala Arg Ala Tyr Pro Ser Asp His Arg Ile Thr Thr Phe 20 25 30

Gln Ser Cys Ala Val Ser Ala Asn Ser Cys Gly Gly Asp Asp Arg Phe

WO 02/103028	PCT/IB02/0418

35	40	45	
Leu Val Gly Arg Gly Val Gl 50 55		His His His His 60	His
His His His His Pro Gl 65 70	n Pro Ala Thr Tyr 75	Gln Thr Ser Gly	Asn 80
Leu Gly Val Ser Tyr Ser Hi 85	s Ser Ser Cys Gly 90	Pro Ser Tyr Gly 95	Ser
Gln Asn Phe Ser Ala Pro Ty 100	r Ser Pro Tyr Ala 105	Leu Asn Gln Glu 110	Ala .
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ttctgttttt ttccccttga agct	tctgtg acctgaagca	tagattactt ttato	gcattg 240
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368

PCT/IB02/04189

WO 02/103028 <212> PRT <213> Homo sapiens <220> <221> MISC FEATURE <222> (20)..(20) $\langle 223 \rangle X = unknown$ <400> 74 Leu Lys His Arg Leu Leu Cys Ile Gly Leu Leu Ser Leu Phe Asn Gly Ala Xaa Cys Cys Leu Met Gln Ser Pro Gln Asn Ile Ser Arg Thr Thr Ser Gln Ile Glu Phe Gln Val Pro His Arg Lys Arg Arg Asp Gln Ala Pro Pro 50

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60

120

720

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119

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	tgtacctgtc					900
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	ttctgggcta					1020
	cgaaggcatt					1080
	atattataac					1140
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<210> 76

<211> 451

<212> PRT

<213> Homo sapiens

<400> 76

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Ala Val Val Gly Thr Gly Leu Asn Val Arg Leu Met Leu Tyr Thr Arg 35 40 45

Lys Asn Leu Thr Cys Ala Gln Thr Ile Asn Ser Ser Ala Phe Gly Asn 50 60

Leu Asn Val Thr Lys Lys Thr Thr Phe Ile Val His Gly Phe Arg Pro 65 70 75 80

Thr Gly Ser Pro Pro Val Trp Met Asp Asp Leu Val Lys Gly Leu Leu 85 90 95

Ser Val Glu Asp Met.Asn Val Val Val Val Asp Trp Asn Arg Gly Ala 100 105 110

Thr Thr Leu Ile Tyr Thr His Ala Ser Ser Lys Thr Arg Lys Val Ala 115 120 125

Met Val Leu Lys Glu Phe Ile Asp Gln Met Leu Ala Glu Gly Ala Ser 130 140

Leu Asp Asp Ile Tyr Met Ile Gly Val Ser Leu Gly Ala His Ile Ser 145 150 155 160

Gly Phe Val Gly Glu Met Tyr Asp Gly Trp Leu Gly Arg Ile Thr Gly 165 170 175

Leu Asp Pro Ala Gly Pro Leu Phe Asn Gly Lys Pro His Gln Asp Arg
180 185 190

Leu Asp Pro Ser Asp Ala Gln Phe Val Asp Val Ile His Ser Asp Thr 195 200 205

- Asp Ala Leu Gly Tyr Lys Glu Pro Leu Gly Asn Ile Asp Phe Tyr Pro 210 215 220
- Asn Gly Gly Leu Asp Gln Pro Gly Cys Pro Lys Thr Ile Leu Gly Gly 225 230 235 240
- Phe Gln Tyr Phe Lys Cys Asp His Gln Arg Ser Val Tyr Leu Tyr Leu 245 250 255
- Ser Ser Leu Arg Glu Ser Cys Thr Ile Thr Ala Tyr Pro Cys Asp Ser 260 265 270
- Tyr Gln Asp Tyr Arg Asn Gly Lys Cys Val Ser Cys Gly Thr Ser Gln 275 280 285
- Lys Glu Ser Cys Pro Leu Leu Gly Tyr Tyr Ala Asp Asn Trp Lys Asp 290 295 300
- His Leu Arg Gly Lys Asp Pro Pro Met Thr Lys Ala Phe Phe Asp Thr 305 310 315 320
- Ala Glu Glu Ser Pro Phe Cys Met Tyr His Tyr Phe Val Asp Ile Ile 325 330 335
- Thr Trp Asn Lys Asn Val Arg Arg Gly Asp Ile Thr Ile Lys Leu Arg 340 345 350
- Asp Lys Ala Gly Asn Thr Thr Glu Ser Lys Ile Asn His Glu Pro Thr 355 360 365
- Thr Phe Gln Lys Tyr His Gln Val Ser Leu Leu Ala Arg Phe Asn Gln 370 375 380
- Asp Leu Asp Lys Val Ala Ala Ile Ser Leu Met Phe Ser Thr Gly Ser 385 390 395 400
- Leu Ile Gly Pro Arg Tyr Lys Leu Arg Ile Leu Arg Met Lys Leu Arg 405 410 415

Ser Leu Ala His Pro Glu Arg Pro Gln Leu Cys Arg Tyr Asp Leu Val 420 425 430

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Leu Gln Leu 450

<210> 77 <211> 2482 <212> DNA <213> Homo sapiens

<400> 77

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<210> 78 <211> 443 <212> PRT <213> Homo sapiens

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His Tyr Asn Tyr Tyr Ala Thr Leu Leu Thr Leu Leu Ile Ala Val Ile 35 40 45

Val Phe Gly Asn Val Leu Val Cys Met Ala Val Ser Arg Glu Lys Ala 50 60

Leu Gln Thr Thr Thr Asn Tyr Leu Ile Val Ser Leu Ala Val Ala Asp 65 70 75 80

Leu Leu Val Ala Thr Leu Val Met Pro Trp Val Val Tyr Leu Glu Val 85 90 95

Val Gly Glu Trp Lys Phe Ser Arg Ile His Cys Asp Ile Phe Val Thr 100 105 110

Leu Asp Val Met Met Cys Thr Ala Ser Ile Leu Asn Leu Cys Ala Ile 115 120 125

Ser Ile Asp Arg Tyr Thr Ala Val Ala Met Pro Met Leu Tyr Asn Thr 130 135 140

Arg Tyr Ser Ser Lys Arg Arg Val Thr Val Met Ile Ser Ile Val Trp 145 150 155 160

Val Leu Ser Phe Thr Ile Ser Cys Pro Leu Leu Phe Gly Leu Asn Asn 165 170 175

Ala Asp Gln Asn Glu Cys Ile Ile Ala Asn Pro Ala Phe Val Val Tyr 180 185 190

Ser Ser Ile Val Ser Phe Tyr Val Pro Phe Ile Val Thr Leu Leu Val 195 200205

Tyr Ile Lys Ile Tyr Ile Val Leu Arg Arg Arg Lys Arg Val Asn 210 215 220

Thr Lys Arg Ser Ser Arg Ala Phe Arg Ala His Leu Arg Ala Pro Leu 225 230 235 240

Lys Gly Asn Cys Thr His Pro Glu Asp Met Lys Leu Cys Thr Val Ile 245 250 255

Met Lys Ser Asn Gly Ser Phe Pro Val Asn Arg Arg Arg Val Glu Ala 260 265 270

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n Glu Leu Glu Met Glu Met Leu Ser Ser Thr Ser $275 \hspace{1.5cm} 280 \hspace{1.5cm} 285 \hspace{1.5cm}$

Pro Pro Glu Arg Thr Arg Tyr Ser Pro Ile Pro Pro Ser His His Gln 290 295 300

Leu Thr Leu Pro Asp Pro Ser His His Gly Leu His Ser Thr Pro Asp 305 310 315 320

Ser Pro Ala Lys Pro Glu Lys Asn Gly His Ala Lys Asp His Pro Lys 325 330 335

Ile Ala Lys Ile Phe Glu Ile Gln Thr Met Pro Asn Gly Lys Thr Arg 340 345 350

Thr Ser Leu Lys Thr Met Ser Arg Arg Lys Leu Ser Gln Gln Lys Glu 355 360 365

Lys Lys Ala Thr Gln Met Leu Ala Ile Val Leu Gly Val Phe Ile Ile 370 375 380

Cys Trp Leu Pro Phe Phe Ile Thr His Ile Leu Asn Ile His Cys Asp 385 390 395 400

Cys Asn Ile Pro Pro Val Leu Tyr Ser Ala Phe Thr Trp Leu Gly Tyr 405 410 415

Val Asn Ser Ala Val Asn Pro Ile Ile Tyr Thr Thr Phe Asn Ile Glu 420 425 430

Phe Arg Lys Ala Phe Leu Lys Ile Leu His Cys 435

<210> 79

<211> 659

<212> DNA

<213> Homo sapiens

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Pro Pro Leu Gly Gly Gln Gln Ser Gln Pro Ser Ala Gly Asp Gly Asn	

Gln Asn Asp Gly Pro Gln Gln Gly Pro Pro Gln Gln Gly Gly Gln Gln

Gln Gln Gly Pro Pro Pro Gln Gly Lys Pro Gln Gly Pro Pro Gln

Gln Gly Gly His Pro Pro Pro Pro Gln Gly Arg Pro Gln Gly Pro Pro

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Gln	Gln	Gly 115	Gly	His	Pro	Arg	Pro 120	Pro	Arg	Gly	Arg	Pro 125	Gln	Gly	Pro	
Pro	Gln 130	Gln	Gly	Gly	His	Gln 135	Gln	Gly	Pro	Pro	Pro 140	Pro	Pro	Pro	ĠĮЯ	
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Gln	Gly	Gln	Ser	Pro 165	Gln											
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ccta	agca	igc o	caggo	ccgg	င် ငင်	caggo	gagct	aca	aacc	ccac	caat	aaaa	act	gatat	aagg	a 540
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<210> 82 <211> 128 <212> PRT <213> Homo sapiens

<400> 82

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Glu Phe Met Lys Leu Leu Gly Ile Ser Ser Asp Val Ile Glu Lys Ala 20 25 30

His Asn Phe Lys Ile Val Thr Glu Val Gln Gln Asp Gly Gln Asp Phe 35 40 45

Thr Trp Ser Gln His Tyr Tyr Gly Gly His Thr Met Thr Asn Lys Phe 50 55 60

Thr Val Gly Lys Glu Ser Asn Ile Gln Thr Met Gly Gly Lys Thr Phe 70 75 80

Lys Ala Thr Val Gln Met Glu Gly Gly Lys Leu Val Val Asn Phe Pro 85 90 95

Asn Tyr His Gln Thr Ser Glu Ile Val Gly Asp Lys Leu Val Glu Val
100 105 110

Ser Thr Ile Gly Gly Val Thr Tyr Glu Arg Val Ser Lys Arg Leu Ala 115 120 125

<210> 83

<211> 1942

<212> DNA

<213> Homo sapiens

<400> 83

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PCT/IB02/04189 WO 02/103028

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<213> Homo sapiens

<400> 84

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- Ala Thr Pro Glu Gln Gly Leu Ser Ala Phe Tyr Leu Ser Tyr Phe Asp 50 55 60
- Met Leu Tyr Pro Glu Asp Ser Ser Trp Ala Ala Lys Ala Pro Gly Ala 65 70 75 80
- Ser Ser Arg Glu Glu Pro Pro Glu Glu Pro Glu Gln Cys Pro Val Ile 85 90 95
- Asp Ser Gln Ala Pro Ala Gly Ser Leu Asp Leu Val Pro Gly Gly Leu 100 105 110
- Thr Leu Glu Glu His Ser Leu Glu Gln Val Gln Ser Met Val Val Gly 115 120 125
- Glu Val Leu Lys Asp Ile Glu Thr Ala Cys Lys Leu Leu Asn Ile Thr 130 135 140
- Ala Asp Pro Met Asp Trp Ser Pro Ser Asn Val Gln Lys Trp Leu Leu 145 150 155 160
- Trp Thr Glu His Gln Tyr Arg Leu Pro Pro Met Gly Lys Ala Phe Gln 165 170 175
- Glu Leu Ala Gly Lys Glu Leu Cys Ala Met Ser Glu Glu Gln Phe Arg 180 185 190
- Gln Arg Ser Pro Leu Gly Gly Asp Val Leu His Ala His Leu Asp Ile 195 200 205
- Trp Lys Ser Ala Ala Trp Met Lys Glu Arg Thr Ser Pro Gly Ala Ile 210 215 220
- His Tyr Cys Ala Ser Thr Ser Glu Glu Ser Trp Thr Asp Ser Glu Val 225 230 235 240

Asp Ser Ser Cys Ser Gly Gln Pro Ile His Leu Trp Gln Phe Leu Lys 245 250 255

Glu Leu Leu Lys Pro His Ser Tyr Gly Arg Phe Ile Arg Trp Leu 260 265 270

Asn Lys Glu Lys Gly Ile Phe Lys Ile Glu Asp Ser Ala Gln Val Ala 275 280 285

Arg Leu Trp Gly Ile Arg Lys Asn Arg Pro Ala Met Asn Tyr Asp Lys 290 295 300

Leu Ser Arg Ser Ile Arg Gln Tyr Tyr Lys Lys Gly Ile Ile Arg Lys 305 310 315 320

Pro Asp Ile Ser Gln Arg Leu Val Tyr Gln Phe Val His Pro Ile 325 330 335

<210> 85

<211> 1224

<212> DNA

<213> Homo sapiens

<400> 85

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120

180

240

300

360

420

480

540

600

660

720

780

132

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<211> 364

<212> PRT

<213> Homo sapiens

<400> 86

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Leu Gly Leu Asp Lys Ala Pro Ser Pro Gln Lys Phe Gln Pro Val Pro 35 40 45

Tyr Ile Leu Lys Lys Ile Phe Gln Asp Arg Glu Ala Ala Ala Thr Thr 50 55 60

Gly Val Ser Arg Asp Leu Cys Tyr Val Lys Glu Leu Gly Val Arg Gly 65 70 75 80

Asn Val Leu Arg Phe Leu Pro Asp Gln Gly Phe Phe Leu Tyr Pro Lys 85 90 95

Lys Ile Ser Gln Ala Ser Ser Cys Leu Gln Lys Leu Leu Tyr Phe Asn 100 105 110

Leu Ser Ala Ile Lys Glu Arg Glu Gln Leu Thr Leu Ala Gln Leu Gly 115 120 125

Leu Asp Leu Gly Pro Asn Ser Tyr Tyr Asn Leu Gly Pro Glu Leu Glu 130 135 140

- Leu Ala Leu Phe Leu Val Gln Glu Pro His Val Trp Gly Gln Thr Thr 145 150 155 160
- Pro Lys Pro Gly Lys Met Phe Val Leu Arg Ser Val Pro Trp Pro Gln 165 170 175
- Gly Ala Val His Phe Asn Leu Leu Asp Val Ala Lys Asp Trp Asn Asp 180 185 190
- Asn Pro Arg Lys Asn Phe Gly Leu Phe Leu Glu Ile Leu Val Lys Glu 195 200 205
- Asp Arg Asp Ser Gly Val Asn Phe Gln Pro Glu Asp Thr Cys Ala Arg 210 215 220
- Leu Arg Cys Ser Leu His Ala Ser Leu Leu Val Val Thr Leu Asn Pro 225 230 235 240
- Asp Gln Cys His Pro Ser Arg Lys Arg Arg Ala Ala Ile Pro Val Pro 245 250 255
- Lys Leu Ser Cys Lys Asn Leu Cys His Arg His Gln Leu Phe Ile Asn. 260 265 270
- Phe Arg Asp Leu Gly Trp His Lys Trp Ile Ile Ala Pro Lys Gly Phe 275 280 285
- Met Ala Asn Tyr Cys His Gly Glu Cys Pro Phe Ser Leu Thr Ile Ser 290 295 300
- Leu Asn Ser Ser Asn Tyr Ala Phe Met Gln Ala Leu Met His Ala Val 305 310 315 320
- Ile Ser Met Leu Tyr Gln Asp Asn Asp Asn Val Ile Leu Arg His 340 345 350

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87

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<210> 88

<211> 210

<212> PRT

<213> Homo sapiens

<400> 88

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- Gly Pro Gly Glu Ala Gly Ala Thr Gly Gly Arg Gly Pro Arg Gly Ala 35 40 45
- Gly Ala Ala Arg Ala Ser Gly Pro Arg Gly Gly Ala Pro Arg Gly Pro 50 55 60
- His Gly Gly Ala Ala Ser Ala Gln Asp Gly Arg Cys Pro Cys Gly Ala 65 70 75 80
- Arg Arg Pro Asp Ser Arg Leu Leu Glu Leu His Ile Thr Met Pro Phe 85 90 95
- Ser Ser Pro Met Glu Ala Glu Leu Val Arg Arg Ile Leu Ser Arg Asp 100 105 110
- Ala Ala Pro Leu Pro Arg Pro Gly Ala Val Leu Lys Asp Phe Thr Val 115 120 125
- Ser Gly Asn Leu Leu Phe Met Ser Val Arg Asp Gln Asp Arg Glu Gly 130 135 140
- Ala Gly Arg Met Arg Val Val Gly Trp Gly Leu Gly Ser Ala Ser Pro 145 150 155 160
- Glu Gly Gln Lys Ala Arg Asp Leu Arg Thr Pro Lys His Lys Val Ser 165 170 175
- Glu Gln Arg Pro Gly Thr Pro Gly Pro Pro Pro Pro Glu Gly Ala Gln 180 185 190
- Gly Asp Gly Cys Arg Gly Val Ala Phe Asn Val Met Phe Ser Ala Pro 195 200 205

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<211> 236

<212> DNA

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

<400> 90

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Ile Arg Arg Thr Pro Ser Gly Arg Ala Lys Pro His Gly Ile Arg Arg 20 25 30

Gly Ser Arg Pro Arg Met Pro Pro Thr His Pro Gln Thr Ser Leu 35 40 45

<210> 91

<211> 1584

<212> DNA

<213> Homo sapiens

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137

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tgtgtgcctg cctgggaaga	cttc				1584

Met Ala Leu Ala Val Ser Leu Pro Leu Ala Cys Arg Ala Arg Leu Leu 5 10 15

Leu Leu Leu Ser Leu Leu Pro Val Ala Arg Ala Ser Glu Ala Glu 20 25 30

His Arg Leu Phe Glu Arg Leu Phe Glu Asp Tyr Asn Glu Ile Ile Arg

Pro Val Ala Asn Val Ser Asp Pro Val Ile Ile His Phe Glu Val Ser 50 55

<210> 92 <211> 502 <212> PRT <213> Homo sapiens

Met Ser Gln Leu Val Lys Val Asp Glu Val Asn Gln Ile Met Glu Thr 65 70 75 80

- Asn Leu Trp Leu Lys Gln Ile Trp Asn Asp Tyr Lys Leu Lys Trp Asn 85 90 95
- Pro Ser Gly Tyr Gly Gly Ala Glu Phe Met Arg Val Pro Ala Gln Lys 100. 105
- Ile Trp Lys Pro Asp Ile Val Leu Tyr Asn Asn Ala Val Gly Asp Phe 115 120 125
- Gln Val Thr Thr Lys Thr Lys Ala Leu Leu Lys Tyr Thr Gly Glu Val 130 135 140
- Thr Trp Ile Pro Pro Ala Ile Phe Lys Ser Ser Cys Lys Ile Asp Val 145 150 155 160
- Thr Tyr Phe Pro Phe Asp Tyr Gln Asn Cys Thr Met Lys Phe Gly Ser 165 170 175
- Trp Ser Tyr Asp Lys Ala Lys Ile Asp Leu Val Leu Ile Gly Ser Ser 180 185 190
- Met Asn Leu Lys Asp Tyr Trp Glu Ser Gly Glu Trp Ala Ile Ile Lys 195 200 205
- Ala Pro Gly Tyr Lys His Asp Ile Lys Tyr Asn Cys Cys Glu Glu Ile 210 215 220
- Tyr Pro Asp Ile Thr Tyr Ser Leu Tyr Ser Arg Arg Leu Pro Leu Phe 225 230 235 240
- Tyr Thr Ile Asn Leu Ile Ile Pro Cys Leu Leu Ile Ser Phe Leu Thr
 245 250 255
- Val Leu Val Phe Tyr Leu Pro Ser Asp Cys Gly Glu Lys Val Thr Leu 260 265 270
- Cys Ile Ser Val Leu Leu Ser Leu Thr Val Phe Leu Leu Val Ile Thr 275 280 285

Glu Thr Ile Pro Ser Thr Ser Leu Val Ile Pro Leu Ile Gly Glu Tyr 290 295 300

Leu Leu Phe Thr Met Ile Phe Val Thr Leu Ser Ile Val Ile Thr Val 305 310 315 320

Phe Val Leu Asn Val His Tyr Arg Thr Pro Thr Thr His Thr Met Pro 325 330 335

Ser Trp Val Lys Thr Val Phe Leu Asn Leu Pro Arg Val Met Phe 340 345 350

Met Thr Arg Pro Thr Ser Asn Glu Gly Asn Ala Gln Lys Pro Arg Pro 355 360 365

Leu Tyr Gly Ala Glu Leu Ser Asn Leu Asn Cys Phe Ser Arg Ala Glu 370 375 380

Ser Lys Gly Cys Lys Glu Gly Tyr Pro Cys Gln Asp Gly Met Cys Gly 385 390 395 400

Tyr Cys His His Arg Arg Ile Lys Ile Ser Asn Phe Ser Ala Asn Leu 405 410 415

Thr Arg Ser Ser Ser Glu Ser Val Asp Ala Val Val Ser Leu Ser 420 425 430

Ala Leu Ser Pro Glu Ile Lys Glu Ala Ile Gln Ser Val Lys Tyr Ile 435 440 445

Ala Glu Asn Met Lys Ala Gln Asn Glu Ala Lys Glu Ile Gln Asp Asp 450 460

Trp Lys Tyr Val Ala Met Val Ile Asp Arg Ile Phe Leu Trp Val Phe 465 470 475 480

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                                                                      120
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Pro Ile Lys Asn Ile Trp Asn Ser His Gly His Leu Ile Ile Phe Arg
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Trp Leu
<210> 95
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<212> DNA
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<222> (439)..(439)
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<213> Homo sapiens

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<221> MISC FEATURE

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 $\langle 223 \rangle$ X = unknown

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Cys Pro Gln Thr Gln Leu Leu Gly Arg Cys Pro Val Thr Ser Ser Leu 20 25 30

Leu Tyr Arg Met Ile Pro Pro Arg Ser Leu Gly Arg Cys Ala Pro Gly 35 40 45

Thr Arg Asp Phe Leu Ser Val Val Ile Arg Gly Glu Met Asp Pro Leu 50 55 60

Ile Gly Ser Phe Leu Met Glu Arg Arg Ala Arg Val Ser Leu Arg Ser 65 70 75 80

Ala Ala Asp Gln Gly Gly Pro Ala Cys Pro Gly Ala Pro Xaa Ala Val 85 90 95

Leu Gly Val Arg Leu Lys Gly Gln Thr Leu Met Ala Tyr Gly
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<210> 97 <211> 3174 <212> DNA <213> Homo sapiens <400> 97

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<211> 700

<212> PRT

<213> Homo sapiens

<400> 98

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Val Ala Ala Gly Ala Phe Ala Asp Leu Arg Ala Leu Arg Ala Leu His 35 40 45

Leu Asp Ser Asn Arg Leu Ala Glu Val Arg Gly Asp Gln Leu Arg Gly 50 55 60

Leu Gly Asn Leu Arg His Leu Ile Leu Gly Asn Asn Gln Ile Arg Arg 65 70 75 80

Val Glu Ser Ala Ala Phe Asp Ala Phe Leu Ser Thr Val Glu Asp Leu 85 90 95

Asp Leu Ser Tyr Asn Asn Leu Glu Ala Leu Pro Trp Glu Ala Val Gly 100 105 110

Gln Met Val Asn Leu Asn Thr Leu Thr Leu Asp His Asn Leu Ile Asp 115 120 125

His Ile Ala Glu Gly Thr Phe Val Gln Leu His Lys Leu Val Arg Leu 130 135 140

Asp Met Thr Ser Asn Arg Leu His Lys Leu Pro Pro Asp Gly Leu Phe 145 150 155 160

Leu Arg Ser Gln Gly Thr Gly Pro Lys Pro Pro Thr Pro Leu Thr Val 165 170 175

Ser Phe Gly Gly Asn Pro Leu His Cys Asn Cys Glu Leu Leu Trp Leu 180 185 190

- Arg Arg Leu Thr Arg Glu Asp Asp Leu Glu Thr Cys Ala Thr Pro Glu 195 200 205
- His Leu Thr Asp Arg Tyr Phe Trp Ser Ile Pro Glu Glu Glu Phe Leu 210 215 220
- Cys Glu Pro Pro Leu Ile Thr Arg Gln Ala Gly Gly Arg Ala Leu Val 225 230 235 240
- Val Glu Gly Gln Ala Val Ser Leu Arg Cys Arg Ala Val Gly Asp Pro 245 250 255
- Glu Pro Val Val His Trp Val Ala Pro Asp Gly Arg Leu Leu Gly Asn 260 265 270
- Ser Ser Arg Thr Arg Val Arg Gly Asp Gly Thr Leu Asp Val Thr Ile 275 280 285
- Thr Thr Leu Arg Asp Ser Gly Thr Phe Thr Cys Ile Ala Ser Asn Ala 290 295 300
- Ala Gly Glu Ala Thr Ala Pro Val Glu Val Cys Val Val Pro Leu Pro 305 310 315 320
- Leu Met Ala Pro Pro Pro Ala Ala Pro Pro Pro Leu Thr Glu Pro Gly 325 330 335
- Ser Ser Asp Ile Ala Thr Pro Gly Arg Pro Gly Ala Asn Asp Ser Ala 340 345 350
- Ala Glu Arg Arg Leu Val Ala Ala Glu Leu Thr Ser Asn Ser Val Leu 355 360 365
- Ile Arg Trp Pro Ala Gln Arg Pro Val Pro Gly Ile Arg Met Tyr Gln 370 375 380
- Val Gln Tyr Asn Ser Ser Val Asp Asp Ser Leu Val Tyr Arg Met Ile 385 390 395 400

Pro Ser Thr Ser Gln Thr Phe Leu Val Asn Asp Leu Ala Ala Gly Arg 405 410 415

- Ala Tyr Asp Leu Cys Val Leu Ala Val Tyr Asp Asp Gly Ala Thr Ala 420 425 430
- Leu Pro Ala Thr Arg Val Val Gly Cys Val Gln Phe Thr Thr Ala Gly 435 440 445
- Asp Pro Ala Pro Cys Arg Pro Leu Arg Ala His Phe Leu Gly Gly Thr 450 455 460
- Met Ile Ile Ala Ile Gly Gly Val Ile Val Ala Ser Val Leu Val Phe 465 470 475 480
- Ile Val Leu Met Ile Arg Tyr Lys Val Tyr Gly Asp Gly Asp Ser 485 490 495
- Arg Arg Val Lys Gly Ser Arg Ser Leu Pro Arg Val Ser His Val Cys 500 505
- Ser Gln Thr Asn Gly Ala Gly Thr Gly Ala Ala Gln Ala Pro Ala Leu 515 , 520 525
- Pro Ala Gln Asp His Tyr Glu Ala Leu Arg Glu Val Glu Ser Gln Ala 530 535 540
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- Ser Ala Glu Pro Glu Val Val Leu Gly Arg Ser Leu Gly Gly Ser Ala 565 570 575
- Thr Ser Leu Cys Leu Leu Pro Ser Glu Glu Thr Ser Gly Glu Glu Ser 580 590
- Arg Ala Ala Val Gly Pro Arg Arg Ser Arg Ser Gly Ala Leu Glu Pro 595 600 605
- Pro Thr Ser Ala Pro Pro Thr Leu Ala Leu Val Pro Gly Gly Ala Ala 610 . 615 620

Ala Arg Pro Arg Pro Gln Gln Arg Tyr Ser Phe Asp Gly Asp Tyr Gly Ala Leu Phe Gln Ser His Ser Tyr Pro Arg Arg Ala Arg Arg Thr Lys 645 650 Arg His Arg Ser Thr Pro His Leu Asp Gly Ala Gly Gly Ala Ala 665 Gly Glu Asp Gly Asp Leu Gly Leu Gly Ser Ala Arg Ala Cys Leu Ala 675 Phe Thr Ser Thr Glu Trp Met Leu Glu Ser Thr Val <210> 99 <211> 697 <212> DNA <213> Homo sapiens <400> 99 gaggccgtga acaaggccct ggagctgtcc ctgcagctca accgcgtctc gctqqaqcqa 60 gactccctgt ctcgggagct gctgcgcgcc atccgccaga aggtggcgct cacgcagqag 120 ctggaggcct ggcaggacga catgcaggtg gtgatcgggc agcagctgcg ctcacagcgc 180 cagaaggage tgagegeete egegtegteg tegacecege geegtgeege geecegette 240 tegeegegee tgggeeeegg geeegeeggt ggetttetea gtaacetett eegaaggace 300 tgacggctgg gcccagaggg ctgcccttgc ccacttaggg gctcactttc ctcttcaggc 360 caatggagcg acagggccca gattgtcttc caaaagaagc tgatgccctc cccgccccag 420 gatgctgggc aagggctcat cgggagcagg ggctcatccg gagcaggggc cagctttgtg 480 gggcaggagc tccaggtggg tggcaggggc aggtqaacaq agctattttc cqaattaata 540 taggtctatc ttttctaggg cagggatggg gctgggtatt tatgtatcaa gatcggacag . 600 agtaatatat aaatcactcc accgatttgg cccccattca tagaaagaaa gagcatggta 660 aaaaagcctg aaactttatt gtaaaaaaaa aaaaaaa 697 <210> 100 <211> 100 <212> PRT

<213>

Homo sapiens

<400> 100

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Gln Lys Val Ala Leu Thr Gln Glu Leu Glu Ala Trp Gln Asp Asp Met 35 40 45

Gln Val Val Ile Gly Gln Gln Leu Arg Ser Gln Arg Gln Lys Glu Leu 50 55 60

Ser Ala Ser Ala Ser Ser Ser Thr Pro Arg Arg Ala Ala Pro Arg Phe 65 70 75 80

Ser Pro Arg Leu Gly Pro Gly Pro Ala Gly Gly Phe Leu Ser Asn Leu 85 90 95

Phe Arg Arg Thr 100

<210> 101

<211> 302

<212> DNA

<213> Homo sapiens

<400> 101

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<211> 38

<212> PRT

<213> Homo sapiens

<400> 102

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<211> 1628

<212> DNA

<213> Homo sapiens

<400> 103

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<211> 214

<212> PRT

<213> Homo sapiens

<400> 104

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His Gly Thr Pro Gly Ser Glu Ala Gly Pro Glu Glu Leu Asn Thr Ser 20 25 30

Val Tyr Gln Pro Ile Asp Gly Ser Pro Asp Tyr Gln Lys Ala Lys Leu 35 40 45

Gln Val Leu Gly Ala Ile Gln Ile Leu Asn Ala Ala Met Ile Leu Ala 50 55 60

Leu Gly Val Phe Leu Gly Ser Leu Gln Tyr Pro Tyr His Phe Gln Lys 65 70 75 80

His Phe Phe Phe Thr Phe Tyr Thr Gly Tyr Pro Ile Trp Gly Ala 85 90 95

Val Phe Phe Cys Ser Ser Gly Thr Leu Ser Val Val Ala Gly Ile Lys 100 105 110

Pro Thr Arg Thr Trp Ile Gln Asn Ser Phe Gly Met Asn Ile Ala Ser 115 120 125

Ala Thr Ile Ala Leu Val Gly Thr Ala Phe Leu Ser Leu Asn Ile Ala 130 135 140

Val Asn Ile Gln Ser Leu Arg Ser Cys His Ser Ser Ser Glu Ser Pro 145 150 155 160

Asp Leu Cys Asn Tyr Met Gly Ser Ile Ser Asn Gly Met Val Ser Leu 165 170 175

Leu Leu Ile Leu Thr Leu Leu Glu Leu Cys Val Thr Ile Ser Thr Ile 180 185 190

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Ser Pro Pro Asn Ser Val 210

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<211> 2011

<212> DNA

<213> Homo sapiens

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<210> 106

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Asn Cys Ser Gln Ser Ile Leu Pro Leu Glu His Gly Ser Ile Tyr Ile 20 25

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<400> 106

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Pro Thr Pro Gly His Leu Ser Pro Leu Val Val His Arg Gln Leu Ser 85 90 95

His Leu Tyr Ala Glu Pro Gln Lys Ser Pro Trp Cys Glu Ala Arg Ser 100 105 110

Leu Glu His Thr Leu Pro Val Asn Arg Glu Thr Leu Lys Arg Lys Val 115 120 125

Ser Gly Asn Arg Cys Ala Ser Pro Val Thr Gly Pro Gly Ser Lys Arg 130 135 140

Asp Ala His Phe Cys Ala Val Cys Ser Asp Tyr Ala Ser Gly Tyr His 145 150 155 160

Tyr Gly Val Trp Ser Cys Glu Gly Cys Lys Ala Phe Phe Lys Arg Ser 165 170 175

Ile Gln Gly His Asn Asp Tyr Ile Cys Pro Ala Thr Asn Gln Cys Thr 180 185 190

Ile Asp Lys Asn Arg Arg Lys Ser Cys Gln Ala Cys Arg Leu Arg Lys 195 200 205

Cys Tyr Glu Val Gly Met Val Lys Cys Gly Ser Arg Arg Glu Arg Cys 210 225 220

Gly Tyr Arg Leu Val Arg Arg Gln Arg Ser Ala Asp Glu Gln Leu His 225 230 235 240

Cys Ala Gly Lys Ala Lys Arg Ser Gly Gly His Ala Pro Arg Val Arg 245 250 255

154

Glu Leu Leu Asp.Ala Leu Ser Pro Glu Gln Leu Val Leu Thr Leu 260 265 270

- Leu Glu Ala Glu Pro Pro His Val Leu Ile Ser Arg Pro Ser Ala Pro 275 280 285
- Phe Thr Glu Ala Ser Met Met Met Ser Leu Thr Lys Leu Ala Asp Lys 290 295 300
- Glu Leu Val His Met Ile Ser Trp Ala Lys Lys Ile Pro Gly Phe Val 305 310 315 320
- Glu Leu Ser Leu Phe Asp Gln Val Arg Leu Leu Glu Ser Cys Trp Met 325 330 335
- Glu Val Leu Met Met Gly Leu Met Trp Arg Ser Ile Asp His Pro Gly 340 345 350
- Lys Leu Ile Phe Ala Pro Asp Leu Val Leu Asp Arg Asp Glu Gly Lys 355 360 365
- Cys Val Glu Gly Ile Leu Glu Ile Phe Asp Met Leu Leu Ala Thr Thr 370 · 375 380
- Ser Arg Phe Arg Glu Leu Lys Leu Gln His Lys Glu Tyr Leu Cys Val 385 390 · 395 400
- Lys Ala Met Ile Leu Leu Asn Ser Ser Met Tyr Pro Leu Val Thr Ala 405 410 415
- Thr Gln Asp Ala Asp Ser Ser Arg Lys Leu Ala His Leu Leu Asn Ala 420 425 430
- Val Thr Asp Ala Leu Val Trp Val Ile Ala Lys Ser Gly Ile Ser Ser 435 440 445
- Gln Gln Ser Met Arg Leu Ala Asn Leu Leu Met Leu Leu Ser His 450 455 460
- Val Arg His Ala Ser Asn Lys Gly Met Glu His Leu Leu Asn Met Lys 465 470 475 480

Cys Lys Asn Val Val Pro Val Tyr Asp Leu Leu Glu Met Leu Asn 485 490 495

Ala His Val Leu Arg Gly Cys Lys Ser Ser Ile Thr Gly Ser Glu Cys 500 505 510

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Ser Gln 530

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Pro Leu Pro Gly Val Phe Gly Gly Ile Gly Asp Pro Val Thr Cys Leu 20 25 30

Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg Tyr Lys 35 40 45

Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys Lys Lys Pro 50 55 60

<210> 119

<211> 582

<212> DNA

<213> Homo sapiens

<400> 119

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<213> Homo sapiens

<400> 120

Met Arg Ala Ser Ser Phe Leu Ile Val Val Phe Leu Ile Ala Gly $1 \hspace{1.5cm} 5 \hspace{1.5cm} 10 \hspace{1.5cm} 15$

Thr Leu Val Leu Glu Ala Ala Val Thr Gly Val Pro Val Lys Gly Gln 20 25 30

Asp Thr Val Lys Gly Arg Val Pro Phe Asn Gly Gln Asp Pro Val Lys 35 40 45

Gly Gln Val Ser Val Lys Gly Gln Asp Lys Val Lys Ala Gln Glu Pro 50 55 60

Val Lys Gly Pro Val Ser Thr Lys Pro Gly Ser Cys Pro Ile Ile Leu 65 70 75 80

Ile Arg Cys Ala Met Leu Asn Pro Pro Asn Arg Cys Leu Lys Asp Thr 85 90 95

Asp Cys Pro Gly Ile Lys Lys Cys Cys Glu Gly Ser Cys Gly Met Ala 100 105 110

Cys Phe Val Pro Gln 115

<210> 121

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<212> DNA

<213> Homo sapiens

<400> 121

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WO 02/103028

WO 02/103028	PCT/IB02/04189

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<210> 123

<211> 388

<212> PRT

<213> Homo sapiens

<400> 123

Met Asp Lys Leu Asp Ala Asn Val Ser Ser Glu Glu Gly Phe Gly Ser 1 5 10 15

Val Glu Lys Val Val Leu Leu Thr Phe Leu Ser Thr Val Ile Leu Met $20 \hspace{1cm} 25 \hspace{1cm} 30$

Ala Ile Leu Gly Asn Leu Leu Val Met Val Ala Val Cys Trp Asp Arg 35 40 45

Gln Leu Arg Lys Ile Lys Thr Asn Tyr Phe Ile Val Ser Leu Ala Phe 50 55 60

Ala Asp Leu Leu Val Ser Val Leu Val Met Pro Phe Gly Ala Ile Glu 65 70 75 80

Leu Val Gln Asp Ile Trp Ile Tyr Gly Glu Val Phe Cys Leu Val Arg 85 90 95

Thr Ser Leu Asp Val Leu Leu Thr Thr Ala Ser Ile Phe His Leu Cys 100 105 110

Cys Ile Ser Leu Asp Arg Tyr Tyr Ala Ile Cys Cys Gln Pro Leu Val 115 120 125

Tyr Arg Asn Lys Met Thr Pro Leu Arg Ile Ala Leu Met Leu Gly Gly 130 135 140

Cys Trp Val Ile Pro Thr Phe Ile Ser Phe Leu Pro Ile Met Gln Gly 145 150 155 160

- Trp Asn Asn Ile Gly Ile Ile Asp Leu Ile Glu Lys Arg Lys Phe Asn 165 170 175
- Gln Asn Ser Asn Ser Thr Tyr Cys Val Phe Met Val Asn Lys Pro Tyr 180 185 190
- Ala Ile Thr Cys Ser Val Val Ala Phe Tyr Ile Pro Phe Leu Leu Met 195 200 205
- Val Leu Ala Tyr Tyr Arg Ile Tyr Val Thr Ala Lys Glu His Ala His 210 215 220
- Gln Ile Gln Met Leu Gln Arg Ala Gly Ala Ser Ser Glu Ser Arg Pro 225 230 235 240
- Gln Ser Ala Asp Gln His Ser Thr His Arg Met Arg Thr Glu Thr Lys 245 250 255
- Ala Ala Lys Thr Leu Cys Ile Ile Met Gly Cys Phe Cys Leu Cys Trp 260 265 270
- Ala Pro Phe Phe Val Thr Asn Ile Val Asp Pro Phe Ile Asp Tyr Thr 275 280 285
- Val Pro Gly Gln Val Trp Thr Ala Phe Leu Trp Leu Gly Tyr Ile Asn 290 295 300
- Ser Gly Leu Asn Pro Phe Leu Tyr Ala Phe Leu Asn Lys Ser Phe Arg 305 310 315 320
- Arg Ala Phe Leu Ile Ile Leu Cys Cys Asp Asp Glu Arg Tyr Arg Arg 325 330 335
- Pro Ser Ile Leu Gly Gln Thr Val Pro Cys Ser Thr Thr Thr Ile Asn 340 345 350
- Gly Ser Thr His Val Leu Arg Asp Ala Val Glu Cys Gly Gln Trp 355 360 365

Glu Ser Gln Cys His Pro Pro Ala Thr Ser Pro Leu Val Ala Ala Gln 370 375 380

Pro Ser Asp Thr 385

<210> 124

<211> 388

<212> PRT

<213> Homo sapiens

<400> 124

Met Asp Lys Leu Asp Ala Asn Val Ser Ser Glu Glu Gly Phe Gly Ser 1 5 10 15

Val Glu Lys Val Val Leu Leu Thr Phe Leu Ser Thr Val Ile Leu Met 20 25 30

Ala Ile Leu Gly Asn Leu Leu Val Met Val Ala Val Cys Trp Asp Arg 35 40 45

Gln Leu Arg Lys Ile Lys Thr Asn Tyr Phe Ile Val Ser Leu Ala Phe 50 55 60

Ala Asp Leu Leu Val Ser Val Leu Val Met Pro Phe Gly Ala Ile Glu 65 70 75 80

Leu Val Gln Asp Ile Trp Ile Tyr Gly Glu Val Phe Cys Leu Val Arg
. 90 95

Thr Ser Leu Asp Val Leu Leu Thr Thr Ala Ser Ile Phe His Leu Cys 100 105 110

Cys Ile Ser Leu Asp Arg Tyr Tyr Ala Ile Cys Cys Gln Pro Leu Val 115 120 125

Tyr Arg Asn Lys Met Thr Pro Leu Arg Ile Ala Leu Met Leu Gly Gly 130 135 140

Cys Trp Val Ile Pro Thr Phe Ile Ser Phe Leu Pro Ile Met Gln Gly 145 150 155 160

Trp Asn Asn Ile Gly Ile Ile Asp Leu Ile Glu Lys Arg Lys Phe Asn

165 170 175

Gln Asn Ser Asn Ser Thr Tyr Cys Val Phe Met Val Asn Lys Pro Tyr 180 185 190

Ala Ile Thr Cys Ser Val Val Ala Phe Tyr Ile Pro Phe Leu Leu Met 195 200 205

Val Leu Ala Tyr Tyr Arg Ile Tyr Val Thr Ala Lys Glu His Ala His 210 215 220

Gln Ile Gln Met Leu Gln Arg Ala Gly Ala Ser Ser Glu Ser Arg Pro 225 230 235 240

Gln Ser Ala Asp Gln His Ser Thr His Arg Met Arg Thr Glu Thr Lys 245 250 255

Ala Ala Lys Thr Leu Cys Ile Ile Met Gly Cys Phe Cys Leu Cys Trp 260 265 270

Ala Pro Phe Phe Val Thr Asn Ile Val Asp Pro Phe Ile Asp Tyr Thr 275 280 285

Val Pro Gly Gln Val Trp Thr Ala Phe Leu Trp Leu Gly Tyr Ile Asn 290 295 300

Ser Gly Leu Asn Pro Phe Leu Tyr Ala Phe Leu Asn Lys Ser Phe Arg 305 310 315 320

Arg Ala Phe Leu Ile Ile Leu Cys Cys Asp Asp Glu Arg Tyr Arg Arg 325 330 335

Pro Ser Ile Leu Gly Gln Thr Val Pro Cys Ser Thr Thr Thr Ile Asn 340 345 350

Gly Ser Thr His Val Leu Arg Asp Ala Val Glu Cys Gly Gln Trp 355 360 365

Glu Ser Gln Cys His Pro Pro Ala Thr Ser Pro Leu Val Ala Ala Gln 370 375 380

Pro Ser Asp Thr

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<210> 126 <211> 925 <212> PRT <213> Homo sapiens

<400> 126

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- Gln Leu Gln Phe Ala Ala Leu Leu Leu Gly Thr Leu Ser Pro Gln Val 20 25 30
- His Thr Leu Arg Pro Glu Asn Leu Leu Leu Val Ser Thr Leu Asp Gly 35 40 45
- Ser Leu His Ala Leu Ser Lys Gln Thr Gly Asp Leu Lys Trp Thr Leu 50 55 60
- Arg Asp Asp Pro Val Ile Glu Gly Pro Met Tyr Val Thr Glu Met Ala 70 75 80
- Phe Leu Ser Asp Pro Ala Asp Gly Ser Leu Tyr Ile Leu Gly Thr Gln 85 90 95
- Lys Gln Leu Gly Leu Met Lys Leu Pro Phe Thr Ile Pro Glu Leu Val 100 105 110
- His Ala Ser Pro Cys Arg Ser Ser Asp Gly Val Phe Tyr Thr Gly Arg 115 120 125
- Lys Gln Asp Ala Trp Phe Val Val Asp Pro Glu Ser Gly Glu Thr Gln 130 135 140
- Met Thr Leu Thr Thr Ala Gly Pro Ser Thr Pro Arg Leu Tyr Ile Gly 145 150 155 160
- Arg Thr Gln Tyr Thr Val Thr Met His Asp Pro Arg Ala Pro Ala Leu 165 170 175
- Arg Trp Asn Thr Thr Tyr Arg Arg Tyr Ser Ala Pro Pro Met Asp Gly
 180 185 190
- Ser Pro Gly Lys Tyr Met Ser His Leu Ala Ser Cys Gly Met Gly Leu 195 200 205
- Leu Leu Thr Val Asp Pro Glu Ser Gly Ala Val Leu Trp Thr Gln Asp 210 215 220

Leu Gly Met Pro Val Met Gly Val Tyr Thr Trp His Gln Asp Gly Leu 225 230 235 240

- Arg Gln Leu Pro His Leu Thr Leu Ala Arg Asp Thr Leu His Phe Leu 245 250 255
- Ala Leu Arg Trp Gly His Ile Arg Leu Pro Ala Ser Gly Pro Gln Asp 260 265 270
- Thr Ala Thr Leu Phe Ser Ala Leu Asp Thr Gln Leu Leu Met Thr Leu 275 280 285
- Tyr Val Gly Lys Asp Glu Thr Gly Phe Tyr Val Ser Lys Ala Leu Val 290 295 300
- His Thr Gly Val Ala Leu Val Pro Arg Gly Leu Thr Leu Ala Pro Thr 305 310 315 320
- Asp Gly Pro Thr Thr Asp Glu Val Thr Leu Gln Val Ser Gly Glu Arg 325 330 335
- Glu Gly Ser Pro Ser Thr Ala Val Arg Tyr Pro Ser Gly Ser Val Ala 340 345 350
- Leu Pro Ser Gln Trp Leu Leu Ile Gly His His Glu Leu Pro Pro Val 355 360 365
- Leu His Thr Thr Met Leu Arg Val His Pro Thr Pro Gly Ser Gly Thr 370 375 380
- Ala Glu Thr Arg Pro Pro Glu Asn Thr Gln Ala Pro Ala Phe Phe Leu 385 390 395 400
- Glu Leu Leu Ser Leu Ser Arg Glu Lys Leu Trp Asp Ser Glu Leu His 405 410 415
- Pro Glu Glu Lys Ile Pro Asp Ser Tyr Leu Gly Leu Gly Pro Gln Asp 420 425 430
- Leu Leu Ala Ala Ser Leu Thr Ala Val Leu Leu Gly Gly Trp Ile Leu 435 440 445

٠.

Phe Val Met Arg Gln Gln Pro Gln Val Val Glu Lys Gln Gln Glu Thr 450 460

- Pro Leu Val Pro Ala Asp Thr Ala Asp Ile Ser Gln Asp Ala Gln Ser 465 470 475 480
- Leu His Ser Gly Val Thr Leu Arg Ser Lys Lys Arg Leu Gln Ser Pro 485 490 . 495
- Ser Lys Gln Ala Gln Pro Leu Asp Asp Pro Glu Ala Glu Gln Leu Thr 500 505 510
- Val Val Gly Lys Ile Ser Phe Asn Pro Lys Asp Val Leu Gly His Gly 515 520 525
- Ala Gly Gly Thr Phe Val Phe Arg Gly Gln Phe Glu Gly Arg Ala Val $530 \hspace{1.5cm} 535 \hspace{1.5cm} 540$
- Ala Val Lys Arg Leu Leu Arg Glu Cys Phe Gly Leu Val Arg Arg Glu 545 550 555 560
- Val Gln Leu Gln Glu Ser Asp Arg His Pro Asn Val Leu Arg Tyr 565 570 575
- Phe Cys Thr Glu Arg Gly Pro Gln Phe His Tyr Ile Ala Leu Glu Leu 580 585 590
- Cys Arg Ala Ser Leu Gln Glu Tyr Val Glu Asn Pro Asp Leu Asp Arg 595 600 605
- Gly Gly Leu Glu Pro Glu Val Val Leu Gln Gln Leu Met Ser Gly Leu 610 620
- Ala His Leu His Ser Leu His Ile Val His Arg Asp Leu Lys Pro Gly 625 630 635 640
- Asn Ile Leu Ile Thr Gly Pro Asp Thr Gln Gly Leu Gly Arg Val Val 645 650 655
- Leu Ser Asp Phe Gly Leu Cys Lys Leu Pro Ala Gly Arg Cys Ser 660 665 670

Phe Ser Leu His Ser Gly Ile Pro Gly Thr Glu Gly Trp Met Ala Pro 675 680 . 685

- Glu Leu Leu Gln Leu Leu Pro Pro Asn Ser Pro Thr Ser Ala Val Asp
 690 695 700
- Ile Phe Ser Ala Gly Cys Val Phe Tyr Tyr Val Leu Ser Gly Gly Ser 705 710 715 720
- His Pro Phe Gly Asp Ser Leu Tyr Arg Gln Ala Asn Ile Leu Thr Gly
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- Val Pro Cys Leu Ala His Leu Glu Glu Glu Val His Asp Lys Val Val 740 745 750
- Ala Arg Asp Leu Val Ala Ala Met Leu Ser Leu Leu Pro Gln Ala Arg 755 760 765
- Pro Ser Ala Pro Gln Val Leu Ala His Pro Phe Phe Trp Ser Arg Ala 770 780
- Lys Gln Leu Gln Phe Phe Gln Asp Val Ser Asp Trp Leu Glu Lys Glu 785 790 795 800
- Ser Glu Gln Glu Pro Leu Met Arg Ala Leu Glu Ala Gly Gly Cys Thr 805 810 815
- Val Val Arg Asp Asn Trp His Glu His Ile Ser Met Pro Leu Gln Ile 820 825 830
- Asp Leu Arg Lys Phe Arg Ser Tyr Lys Gly Thr Ser Val Arg Asp Leu 835 840 845
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- Glu Val Arg Gln Ala Leu Gly Gln Val Pro Asp Gly Phe Val Gln Tyr 865 870 875 880
- Phe Thr Asn Arg Phe Pro Gln Leu Leu His Thr His Arg Val Met 885 890 895

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- Ser Ser Gly Asn Ser Ser Pro Glu Tyr Pro Arg Lys Glu Phe Ala Ser 115 120 125
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- Arg Leu Gln Ser Ala Ser Pro Ser Thr Arg Trp Thr Glu Leu Asp Asp 145 150 155 160
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- Tyr Gly Val Lys Lys Asn Met Pro Gln Ser Pro Ala Ala Val Asn Thr 305 310 315
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Cys Thr Lys Asn Gln Leu Val Leu Ile Val Asn Glu Asn Pro Ala Ser 80

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Ala Ala Ser Ser Thr Ser Gly Pro Gln Pro Pro Pro Gln Ser Leu 50 55 60

Asn Leu Leu Ser Gln Ala Gln Leu Gln Ala Gln Leu Ile Ala Pro Gly 65 70 75 80

Gly Thr Gln Met Lys Lys Ser Gly Phe Gln Ile Thr Ser Val Thr 85 90 95

Pro Ala Gln Ile Ser Ala Ser Ile Ser Ser Asn Asn Ser Ile Ala Glu 100 105 110

Asp Thr Glu Ser Tyr Asp Asp Leu Asp Glu Ser His Thr Glu Asp Leu 115 120 125

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<211> 60

<212> PRT

<213> Homo sapiens

<400> 136

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1 5 10 15

His Ile Asp Arg His Leu Ser Asn Phe Lys Ser Phe Thr Ile Ala Asn $20 \hspace{1cm} 25 \hspace{1cm} 30$

Asn Ala Ala Thr Gln Leu Phe Thr Cys Ala Phe Leu His Met Gly Lys 35 40 45

His Ser Ser Arg Lys Gln Glu Ile Lys Leu Leu Gly 50 55 60

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<213> Homo sapiens

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<400> 139

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Glu Ala Gly Pro Glu Lys Ala Lys Leu Lys Ser Phe Ser Ala Lys Ile

Val Gln Leu Leu Lys Glu Trp Thr Glu Ala Phe Pro Tyr Asp Phe Gln

Asp Glu Lys Ala Met Ala Glu Leu Lys Ala Ile Thr His Arg Val Thr

Gln Cys Asp Glu Glu Asn Gly Thr Val Lys Lys Ala Ile Ala Gln Met 105

Thr Gln Ser Leu Leu Ser Leu Ala Ala Arg Ser Gln Leu Gln Glu 115 120 125

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- Lys Thr Lys Pro Pro Ala Ala Gln Lys Asp Ile Leu Gly Val Cys Cys 145 150 155 160
- Asp Pro Leu Val Leu Ala Gln Gln Leu Thr His Ile Glu Leu Asp Arg 165 170 175
- Val Ser Ser Ile Tyr Pro Glu Asp Leu Met Gln Ile Val Ser His Met 180 185 190
- Asp Ser Leu Asp Asn His Arg Cys Arg Gly Asp Leu Thr Lys Thr Tyr 195 200 205
- Ser Leu Glu Ala Tyr Asp Asn Trp Phe Asn Cys Leu Ser Met Leu Val 210 215 220
- Ala Thr Glu Val Cys Arg Val Val Lys Lys His Arg Thr Arg Met 225 230 235 240
- Leu Glu Phe Phe Ile Asp Val Ala Arg Glu Cys Phe Asn Ile Gly Asn 245 250 255
- Phe Asn Ser Met Met Ala Ile Ile Ser Gly Met Asn Leu Ser Pro Val 260 265 270
- Ala Arg Leu Lys Lys Thr Trp Ser Lys Val Lys Thr Ala Lys Phe Asp 275 280 285
- Val Leu Glu His His Met Asp Pro Ser Ser Asn Phe Cys Asn Tyr Arg
 290 295 300
- Thr Ala Leu Gln Gly Ala Thr Gln Arg Ser Gln Met Ala Asn Ser Ser 305 310 315 320
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Tyr Phe Leu His Lys Ile His Thr Asn His Leu Pro Asn Gly His Ile 340 345 350

Asn Phe Lys Lys Phe Trp Glu Ile Ser Arg Gln Ile His Glu Phe Met 355 360 365

Thr Trp Thr Gln Val Glu Cys Pro Phe Glu Lys Asp Lys Lys Ile Gln 370 375 380

Ser Tyr Leu Leu Thr Ala Pro Ile Tyr Ser Glu Glu Ala Leu Phe Val 385 390 395 400

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<211> 45

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Arg Leu Tyr Ala Ser Thr Glu Lys Asn His Val Ile His
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<210> 143

<211> 97

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<213> Homo sapiens

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Leu Leu Val Gln Pro Leu Leu Leu Ala Ser Gln Met Cys Leu $\overline{\text{Val}}$ 50 55 60

208

Val Glu 65	Val	Glu	Glu	Glu 70	Asn	Glu	Glu	Ala	Glu 75	Gly	Leu	Gln	Glu	His 80	
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aacttgt															180
gatcttt															240
tgaaaca														-	300
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- Ser Thr Ser Glu Phe Thr Thr Glu Ser Phe Thr Arg Gly Ser Thr Ser 210 215 220
- Thr Asn Ala Ile Leu Thr Ser Phe Ser Thr Ile Ile Trp Ser Ser Thr 225 230 235 240
- Pro Thr Ile Ile Met Ser Ser Ser Pro Ser Ser Ala Ser Ile Thr Pro
 245 250 255
- Val Phe Ala Thr Thr Ile His Ser Val Pro Ser Ser Pro Tyr Ile Phe 260 265 270
- Ser Thr Glu Asn Val Gly Ser Ala Ser Ile Thr Ala Phe Pro Ser Leu 275 280 285
- Ser Ser Ser Ser Thr Thr Ser Thr Ser Pro Thr Ser Ser Ser Leu Thr 290 295 300
- Thr Ala Leu Thr Glu Ile Thr Pro Phe Ser Tyr Ile Ser Leu Pro Ser 305 310 315 320
- Thr Thr Pro Cys Pro Gly Thr Ile Thr Ile Thr Ile Val Pro Ala Ser 325 330 335

Pro Thr Asp Pro Cys Val Glu Met Asp Pro Ser Thr Glu Ala Thr Ser 340 345 350

- Pro Pro Thr Thr Pro Leu Thr Val Phe Pro Phe Thr Thr Glu Met Val 355 360 365
- Thr Cys Pro Ser Ser Ile Ser Met Gln Thr Thr Leu Ala Thr His Met 370 375 380
- Asp Thr Ser Ser Met Thr Pro Glu Ser Glu Ser Ser Ile Ile Pro Asn 385 390 395 400
- Ala Ser Ser Ser Thr Gly Thr Gly Thr Val Pro Thr Asn Thr Val Phe $405 \hspace{1cm} 410 \hspace{1cm} 415$
- Thr Ser Thr Arg Leu Pro Thr Ser Glu Thr Trp Leu Ser Asn Asn Ser 420 425 430
- Val Ile Pro Thr Pro Leu Pro Gly Val Ser Thr Ile Pro Leu Thr Met 435 440 445
- Lys Pro Ser Ser Ser Leu Pro Thr Ile Leu Arg Thr Ser Ser Lys Ser 450 455 460
- Thr His Pro Ser Pro Pro Thr Ala Arg Thr Ser Glu Thr Ser Val Ala 465 470 475 480
- Thr Thr Gln Thr Pro Thr Thr Leu Thr Thr Arg Arg Thr Thr Pro Ile 485 490 495
- Thr Ser Trp Met Thr Thr Gln Ser Thr Leu Thr Thr Thr Ala Gly Thr 500 505 510
- Cys Asp Asn Gly Gly Thr Trp Glu Gln Gly Gln Cys Ala Cys Leu Pro 515 520 525
- Gly Phe Ser Gly Asp Arg Cys Gln Leu Gln Thr Arg Cys Gln Asn Gly 530 540
- Gly Gln Trp Asp Gly Leu Lys Cys Gln Cys Pro Ser Thr Phe Tyr Gly 545 550 555 560

Ser Ser Cys Glu Phe Ala Val Glu Gln Val Asp Leu Asp Val Val Glu 565 570 575

- Thr Glu Val Gly Met Glu Val Ser Val Asp Gln Gln Phe Ser Pro Asp 580 585 590
- Leu Asn Asp Asn Thr Ser Gln Ala Tyr Arg Asp Phe Asn Lys Thr Phe 595 600 605
- Trp Asn Gln Met Gln Lys Ile Phe Ala Asp Met Gln Gly Phe Thr Phe 610 620
- Lys Gly Val Glu Ile Leu Ser Leu Arg Asn Gly Ser Ile Val Val Asp 625 630 635 640
- Tyr Leu Val Leu Glu Met Pro Phe Ser Pro Gln Leu Glu Ser Glu 645 650 655
- Tyr Glu Gln Val Lys Thr Thr Leu Lys Glu Gly Leu Gln Asn Ala Ser 660 655 670
- Gln Asp Ala Asn Ser Cys Gln Asp Ser Gln Thr Leu Cys Phe Lys Pro 675 680 685
- Asp Ser Ile Lys Val Asn Asn Ser Lys Thr Glu Leu Thr Pro Glu 690 695 700
- Ala Ile Cys Arg Arg Ala Ala Pro Thr Gly Tyr Glu Glu Phe Tyr Phe 705 710 715 720
- Pro Leu Val Glu Ala Thr Arg Leu Arg Cys Val Thr Lys Cys Thr Ser 725 730 735
- Gly Val Asp Asn Ala Ile Asp Cys His Gln Gly Gln Cys Val Leu Glu 740 745 750
- Thr Ser Gly Pro Ala Cys Arg Cys Tyr Ser Thr Asp Thr His Trp Phe 755 760 765
- Ser Gly Pro Arg Cys Glu Val Ala Val His Trp Arg Ala Leu Val Gly 770 780

Gly Leu Thr Ala Gly Ala Ala Leu Leu Val Leu Leu Leu Leu Ala Leu 785 790 795 800	
Gly Val Arg Ala Val Arg Ser Gly Trp Trp Gly Gly Gln Arg Arg Gly 805 810 815	
Arg Ser Trp Asp Gln Asp Arg Lys Trp Phe Glu Thr Trp Asp Glu Glu 820 825 830	
Val Val Gly Thr Phe Ser Asn Trp Gly Phe Glu Asp Asp Gly Thr Asp 835 840 845	
Lys Asp Thr Asn Phe His Val Ala Leu Glu Asn Val Asp Thr Thr Met 850 855 860	
Lys Val His Ile Lys Arg Pro Glu Met Thr Ser Ser Ser Val 865 870 875	
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gtaggaagaa aaagatacaa gaaaaataca teetagaaet eattateaaa attattggtg	420
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227

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<211> 564

<212> PRT

<213> Homo sapiens

<400> 176

WO 02/103028

20 25 30

PCT/IB02/04189

Tyr Glu Lys Ala Asp Lys Tyr Tyr Tyr Thr Arg Lys Ile Leu Gly Ser 35 40 45

Thr Leu Ala Cys Ala Arg Ala Ser Ala Leu Cys Leu Asn Phe Asn Ser 50 55 60

Thr Leu Ile Leu Leu Pro Val Cys Arg Asn Leu Leu Ser Phe Leu Arg 65 70 75 80

Gly Thr Cys Ser Phe Cys Ser Arg Thr Leu Arg Lys Gln Leu Asp His 85 90 95

Asn Leu Thr Phe His Lys Leu Val Ala Tyr Met Ile Cys Leu His Thr 100 105 110

Ala Ile His Ile Ile Ala His Leu Phe Asn Phe Asp Cys Tyr Ser Arg 115 120 125

Ser Arg Gln Ala Thr Asp Gly Ser Leu Ala Ser Ile Leu Ser Ser Leu 130 135 140

Ser His Asp Glu Lys Lys Gly Gly Ser Trp Leu Asn Pro Ile Gln Ser 145 150 155 160

Arg Asn Thr Thr Val Glu Tyr Val Thr Phe Thr Ser Val Ala Gly Leu 165 170 175

Thr Gly Val Ile Met Thr Ile Ala Leu Ile Leu Met Val Thr Ser Ala 180 185 190

Thr Glu Phe Ile Arg Arg Ser Tyr Phe Glu Val Phe Trp Tyr Thr His 195 200 205

His Leu Phe Ile Phe Tyr Ile Leu Gly Leu Gly Ile His Gly Ile Gly 210 215 220

Gly Ile Val Arg Gly Gln Thr Glu Glu Ser Met Asn Glu Ser His Pro 225 230 235 240

Arg Lys Cys Ala Glu Ser Phe Glu Met Trp Asp Asp Arg Asp Ser His

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PCT/IB02/04189

245 250 255 Cys Arg Arg Pro Lys Phe Glu Gly His Pro Pro Glu Ser Trp Lys Trp 270 265 Ile Leu Ala Pro Val Ile Leu Tyr Ile Cys Glu Arg Ile Leu Arg Phe 280 Tyr Arg Ser Gln Gln Lys Val Val Ile Thr Lys Val Val Met His Pro 295 290 Ser Lys Val Leu Glu Leu Gln Met Asn Lys Arg Gly Phe Ser Met Glu 310 Val Gly Gln Tyr Ile Phe Val Asn Cys Pro Ser Ile Ser Leu Leu Glu 330 Trp His Pro Phe Thr Leu Thr Ser Ala Pro Glu Glu Asp Phe Phe Ser Ile His Ile Arg Ala Ala Gly Asp Trp Thr Glu Asn Leu Ile Arg Ala Phe Glu Gln Gln Tyr Ser Pro Ile Pro Arg Ile Glu Val Asp Gly Pro 375 380 Phe Gly Thr Ala Ser Glu Asp Val Phe Gln Tyr Glu Val Ala Val Leu 390 385

Val Gly Ala Gly Ile Gly Val Thr Pro Phe Ala Ser Ile Leu Lys Ser

Ile Trp Tyr Lys Phe Gln Cys Ala Asp His Asn Leu Lys Thr Lys Lys

Ile Tyr Phe Tyr Trp Ile Cys Arg Glu Thr Gly Ala Phe Ser Trp Phe

Asn Asn Leu Leu Thr Ser Leu Glu Gln Glu Met Glu Glu Leu Gly Lys

Val Gly Phe Leu Asn Tyr Arg Leu Phe Leu Thr Gly Trp Asp Ser Asn

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480 475 470 465

Ile Val Gly His Ala Ala Leu Asn Phe Asp Lys Ala Thr Asp Ile Val 490

Thr Gly Leu Lys Gln Lys Thr Ser Phe Gly Arg Pro Met Trp Asp Asn 505 500

Glu Phe Ser Thr Ile Ala Thr Ser His Pro Lys Ser Val Val Gly Val 520 515

Phe Leu Cys Gly Pro Arg Thr Leu Ala Lys Ser Leu Arg Lys Cys Cys 535

His Arg Tyr Ser Ser Leu Asp Pro Arg Lys Val Gln Phe Tyr Phe Asn 555

Lys Glu Asn Phe

<210> 177

<211> 191 <212> PRT

<213> Homo sapiens

<400> 177

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Tyr Glu Lys Ala Asp Lys Tyr Tyr Tyr Thr Arg Lys Ile Leu Gly Ser 40 35

Thr Leu Ala Cys Ala Arg Ala Ser Ala Leu Cys Leu Asn Phe Asn Ser

Thr Leu Ile Leu Leu Pro Val Cys Arg Asn Leu Leu Ser Phe Leu Arg 75 65 70

Gly Thr Cys Ser Phe Cys Ser Arg Thr Leu Arg Lys Gln Leu Asp His 90

Asn Leu Thr Phe His Lys Leu Val Ala Tyr Met Ile Cys Leu His Thr 100 105 110

Ala Ile His Ile Ile Ala His Leu Phe Asn Phe Asp Cys Tyr Ser Arg 115 120 125

Ser Arg Gln Ala Thr Asp Gly Ser Leu Ala Ser Ile Leu Ser Ser Leu 130 135 140

Ser His Asp Glu Lys Lys Gly Gly Ser Trp Leu Asn Pro Ile His Pro 145 150 155 160

His Ile Thr Pro Thr Val Tyr Met Phe Thr Val Thr Phe Asp Met Val 165 170 175

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<212> DNA

<213> Homo sapiens

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<210> 179

<211> 341

<212> PRT

<213> Homo sapiens

<400> 179

Met Glu Pro Ala Phe Gly Glu Val Asn Gln Leu Gly Gly Val Phe Val $1 \hspace{1cm} 5 \hspace{1cm} 10 \hspace{1cm} 15$

Asn Gly Arg Pro Leu Pro Asn Ala Ile Arg Leu Arg Ile Val Glu Leu 20 25 30

Ala Gln Leu Gly Ile Arg Pro Cys Asp Ile Ser Arg Gln Leu Arg Val $35 \hspace{1cm} 40 \hspace{1cm} . \hspace{1cm} 45$

Ser His Gly Cys Val Ser Lys Ile Leu Ala Arg Tyr Asn Glu Thr Gly 50 60

Ser Ile Leu Pro Gly Ala Ile Gly Gly Ser Lys Pro Arg Val Thr Thr 65 70 75 80

- Pro Thr Val Val Lys His Ile Arg Thr Tyr Lys Gln Arg Asp Pro Gly 85 90 95
- Ile Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu Ala Asp Gly Val Cys 100 105 110
- Asp Lys Tyr Asn Val Pro Ser Val Ser Ser Ile Ser Arg Ile Leu Arg 115 120 125
- Asn Lys Ile Gly Asn Leu Ala Gln Gln Gly His Tyr Asp Ser Tyr Lys 130 135 140
- Gln His Gln Pro Thr Pro Gln Pro Ala Leu Pro Tyr Asn His Ile Tyr 145 150 155 160
- Ser Tyr Pro Ser Pro Ile Thr Ala Ala Ala Ala Lys Val Pro Thr Pro 165 170 175
- Pro Gly Val Pro Ala Ile Pro Gly Ser Val Ala Met Pro Arg Thr Trp 180 185 190
- Pro Ser Ser His Ser Val Thr Asp Ile Leu Gly Ile Arg Ser Ile Thr 195 200 205
- Asp Gln Val Ser Asp Ser Ser Pro Tyr His Ser Pro Lys Val Glu Glu 210 215 220
- Trp Ser Ser Leu Gly Arg Asn Asn Phe Pro Ala Ala Ala Pro His Ala 225 230 . 235 240
- Val Asn Gly Leu Glu Lys Gly Ala Leu Glu Gln Glu Ala Lys Tyr Gly 245 250 255
- Gln Ala Pro Asn Gly Leu Pro Ala Val Gly Ser Phe Val Ser Ala Ser 260 265 270
- Ser Met Ala Pro Tyr Pro Thr Pro Ala Gln Val Ser Pro Tyr Met Thr 275 280 285

Tyr Ser Ala Ala Pro Ser Gly Tyr Val Ala Gly His Gly Trp Gln His 290 295 300

Ala Gly Gly Thr Ser Leu Ser Pro His Asn Cys Asp Ile Pro Ala Ser 305 310 315 320

Leu Ala Phe Lys Gly Met Gln Ala Ala Arg Glu Gly Ser His Ser Val 325 330 335

Thr Ala Ser Ala Leu 340

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<211> 1253

<212> DNA

<213> Homo sapiens

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<210> 181

<211> 320

<212> PRT

<213> Homo sapiens

<400> 181

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Ser Ser Gly Leu Arg Gly Leu Trp Asp Cys Leu Pro Ala Asp Leu Val 20 25 30

Gly Glu Arg Ser Ala Gln Ser Lys Ala Ala Glu Ser Leu Glu Glu Leu 35 40 45

Arg Ala Cys Ile Ser Thr Leu Val Asp Arg His Arg Glu Ala Gln Gln 50 55 60

Val Leu Ala Arg Leu Gln Glu Glu Asn Gln Gln Leu Arg Gly Ser Leu 65 70 75 80

Ser Pro Cys Arg Glu Pro Gly Thr Ser Leu Lys Ala Pro Ala Ser Pro 85 90 95

Gln Val Ala Ala Leu Glu Gln Asp Leu Gly Lys Leu Glu Glu Glu Leu 100 105 110

Arg Ala Val Gln Ala Thr Met Ser Gly Lys Ser Gln Glu Ile Gly Lys 115 120 125

Leu Lys Gln Leu Leu Tyr Gln Ala Thr Glu Glu Val Ala Glu Leu Arg 130 135 140

Ala Arg Glu Ala Ala Ser Leu Arg Gln His Glu Lys Thr Arg Gly Ser 145 150 155 160

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- Asn Ile Ala Ala Glu Thr Arg Ala Glu Asp Pro Pro Trp Phe Glu Gly 130 135
- Leu Glu Ser Arg Phe Gln Ser Lys Ser Gly Tyr Leu Arg Tyr Ser Cys 145 150 155 160
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- Ser Ser Leu Gly Met Pro Ala His Pro Ser Met Leu Pro Val Ser His 325 330 335
- Asn Ala Ser Pro Pro Thr Ser Ser Ser Gln Tyr Pro Ser Leu Trp Ser 340 \cdot 345 \cdot 350

Val Ser Asn Gly Ala Val Thr Pro Gly Ser Gln Ala Ala Ala Val Ser 355 360 365

Asn Gly Leu Gly Ala Gln Phe Phe Arg Gly Ser Pro Ala His Tyr Thr 370 375 380

Pro Leu Thr His Pro Val Ser Ala Pro Ser Ser Ser Gly Ser Pro Leu 385 390 395 400

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<400> 204

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Ala Gly Thr Gly Gly Ala Gly Gly Asp Val Ala Gly Pro Ala Gly Ala 35 40 45

Thr Ala Ile Pro Gly Ala Arg Lys Val Pro Leu Arg Ala Arg Asn Leu 50 55 60

Pro Pro Ser Phe Phe Thr Glu Pro Ser Arg Ala Gly Gly Gly Arg Val 70 75 80

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•	3	3 5 - 5 - 5 -	3.33	3	3 -:	
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taggattaga	ggcccaagcc	actataceta	atcaaatatc	tttgagagtg	atactatece	360
caggactaca	ggcccaagcc	accycycccy	gccaggcgcc	cccgagagcg	gegetaceee	500
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430

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<213> Homo sapiens

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aagaaaagta gttatttaga accattgtgt atgtttaaag	cacggtacaa atatagcaca	180
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	Thr	Phe	Pro 35	Lys	Pro	Lys	Asn	Ser 40	Ala	Leu	Gln	Glu	Lys 45	Ile	Ala	Ala	
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	1	111	, 1113	1172	5	чэр	rity	ΩCI	1111	10	***	, 11. Y	Lou	2110	15		
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tttctaaaaa gtaatgtatt ctcttaaaac aatggctttt ctcttttgca aaagcacagc	180
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Lys	His 50	Ser	Glu	Ala	Arg	Arg 55	Arg	Leu	Pro	Glu	Pro 60	Arg	Gln	Leu	His		
Leu 65	Gln	Pro	Val	Gly	Ala 70	Asn	Ser	Val	Glu	Arg 75	Ala	Ala	Arg	Arg	Arg 80		
Arg	Thr	Arg	Pro	Glu 85	Pro	Gly	Pro	Ala	Arg 90	Arg	Gly	Ala	Arg	Ala 95	Glu		
Pro	Pro	Gly	Pro 100	Pro	Thr	Leu	Gln	Asp 105	Pro	Pro	Ala	Ser	His 110		Gly		
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Gly 145	Gly	Leu	Ile	Gly	Ser 150	Asp	Ser	Leu	Pro	Pro 155	Ala	Asp	Pro	Leu	Arg 160		
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Leu Asp
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                                                                         180
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totaaaaaca acattqctqc tqattttcaa gtaagctgcc tcttctacat agcaaatagg
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<211> 438

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<213> Homo sapiens

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His Lys Ala Cys Ser Gly Val Trp Asp Asn Ile Thr Cys Trp Arg Pro 50 60

Ala Asn Val Gly Glu Thr Val Thr Val Pro Cys Pro Lys Val Phe Ser 65 70 75 80

Asn Phe Tyr Ser Lys Ala Gly Asn Ile Ser Lys Asn Cys Thr Ser Asp 85 90 95

Gly Trp Ser Glu Thr Phe Pro Asp Phe Val Asp Ala Cys Gly Tyr Ser 100 105 110

Asp Pro Glu Asp Glu Ser Lys Ile Thr Phe Tyr Ile Leu Val Lys Ala 115 120 125

Ile Tyr Thr Leu Gly Tyr Ser Val Ser Leu Met Ser Leu Ala Thr Gly 130 140

Ser Ile Ile Leu Cys Leu Phe Arg Lys Leu His Cys Thr Arg Asn Tyr 145 150 155 160

Ile His Leu Asn Leu Phe Leu Ser Phe Ile Leu Arg Ala Ile Ser Val 165 170 175

Leu Val Lys Asp Asp Val Leu Tyr Ser Ser Ser Gly Thr Leu His Cys 180 185 190

- Pro Asp Gln Pro Ser Ser Trp Val Gly Cys Lys Leu Ser Leu Val Phe 195 200 205
- Leu Gln Tyr Cys Ile Met Ala Asn Phe Phe Trp Leu Leu Val Glu Gly 210 215 220
- Leu Tyr Leu His Thr Leu Leu Val Ala Met Leu Pro Pro Arg Arg Cys 225 230 235 240
- Phe Leu Ala Tyr Leu Leu Ile Gly Trp Gly Leu Pro Thr Val Cys Ile 245 250 255
- Gly Ala Trp Thr Ala Ala Arg Leu Tyr Leu Glu Asp Thr Gly Cys Trp 260 265 270
- Asp Thr Asn Asp His Ser Val Pro Trp Trp Val Ile Arg Ile Pro Ile 275 280 285
- Leu Ile Ser Ile Ile Val Asn Phe Val Leu Phe Ile Ser Ile Ile Arg 290 295 300
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- Ser Gln Tyr Lys Arg Leu Ala Lys Ser Thr Leu Leu Leu Ile Pro Leu 325 330 335
- Phe Gly Val His Tyr Met Val Phe Ala Val Phe Pro Ile Ser Ile Ser 340 345 350
- Ser Lys Tyr Gln Ile Leu Phe Glu Leu Cys Leu Gly Ser Phe Gln Gly 355 360 365
- Leu Val Val Ala Val Leu Tyr Cys Phe Leu Asn Ser Glu Val Gln Cys 370 380
- Glu Leu Lys Arg Lys Trp Arg Ser Arg Cys Pro Thr Pro Ser Ala Ser 385 390 395 400

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Pro Ala Asp Ala Ala Pro Asp Phe Pro Ala Gly Gly Pro Pro Pro Ala 50 55

Ala Ala Ala Ala Thr Ala Tyr Gly Pro Asp Ala Arg Pro Gly Gln 65

Ser Pro Gly Arg Leu Glu Ala Leu Gly Gly Arg Leu Gly Arg Lys 90

Gly Ser Gly Pro Lys Lys Glu Arg Arg Arg Thr Glu Ser Ile Asn Ser 105

Ala Phe Ala Glu Leu Arg Glu Cys Ile Pro Asn Val Pro Ala Asp Thr 120 Lys Leu Ser Lys Ile Lys Thr Leu Arg Leu Ala Thr Ser Tyr Ile Ala Tyr Leu Met Asp Val Leu Ala Lys Asp Ala Gln Ser Gly Asp Pro Glu Ala Phe Lys Ala Glu Leu Lys Lys Ala Asp Gly Gly Arg Glu Ser Lys Arg Lys Arg Glu Leu Gln Gln His Glu Gly Phe Pro Pro Ala Leu Gly 185 Pro Val Glu Lys Arg Ile Lys Gly Arg Thr Gly Trp Pro Gln Gln Val 200 Trp Ala Leu Glu Leu Asn Gln 210 <210> 240 <211> 489 <212> DNA <213> Homo sapiens <400> 240 60 tttccctact cattagctgg ccccttttat gaccaatgac tcataaggca agatgtgtgg tggcatcttc ggacaggcgg caggctttaa tagggcagcc tgggttggtg gaggcaagca 120 aagctaattg gcatgcgtgg gaatcaaacc ccaggccctg ggctcattag cccatggtca 180 aaacaactga gccagaggag gtaataattt gcccaagaat atcagtagtt cctttattag 240 300 aagaaaatgg ctgatatgga agttggggaa tctgaattgc cagagaatct tgggaagagt 360 aataagctct tagtctcaac aaaaagtgtt ttttcatctc agcgcgtaaa gggtgctata 420 tgggaacaaa gaagtatttt aaaattataa ctactcattc tttctttagc cttagttaat ttgagcagaa gccacaacaa gcaaaccaca ataaatttag aattggcaga aatccacatt 480 aactcctct 489 <210> 241

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His Leu Trp Asn Pro Gln Ser Ser Thr His Lys Thr Asp Gly Val Ser 20 25 30

Leu Trp Ala Gly Arg Gly Glu Ala Arg His Ser Ala Ser Leu Trp Lys 35 40 45

Pro Arg Gln Arg Leu Ser Lys Pro His Ser Tyr Ala Gln Ser Leu Ile 50 55 60

Pro Phe Leu Glu Leu Glu Leu Met Pro Ser Val Ala Leu Gly Phe Ser 65 70 75 80

Pro Phe Gly Ser Phe Asp Arg Arg Asn Pro Thr Gln Arg Leu Ala Ala 85 90 95

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Arg Thr Leu Ala Gly Glu Thr Gly Thr Glu Ser Ala Pro Leu Gly Gly 35 40 45

Val Leu Thr Thr Pro His Asn Ile Ser Ser Leu Ser Pro Arg Gln Leu 50 55 60

Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu Arg Val 65 70 75 80

Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu Ser Thr 85 90 95

Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro Glu Asp 100 105 110

Leu Asp Ala Leu Pro Leu Asp Leu Leu Phe Leu Asn Pro Asp Ala 115 120 125

Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile Thr Lys 130 135 140

Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln Arg Leu 145 150 155 160

Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu Leu Ser 165 170 175

Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu Pro Gly 180 185 190

Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu Val Ser 195 200 205

Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg Ala Ala 210 215 220

Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp Ser Val 225 230 235 240

Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly Gln Pro 245 250 255

Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg Gln Arg 260 265 270

Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile Leu Arg 275 280 285

Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser Gly Lys 290 295 300

Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys Trp Glu 305 310 315 320

Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met Asp Arg 325 330 335

Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu Lys His 340 345 350

Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val Ile Gln 355 360 365

His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile Arg Lys 370 375 380

Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu Val Asp 385 390 395 400

Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu Pro Gln 405 410 415

Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln Leu Asp 420 425 430

Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys

Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser Ile Trp

Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp 470

Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn Gly Ser 485 490

Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu 500 505

Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu Ala Thr 515 520 525

Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val Ala Glu 530 535

Val Gln Lys Leu Gly Pro His Val Glu Gly Leu Lys Ala Glu Glu 545 550 555

Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp 565 570 575

Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr 580

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Cys Gly His Met Tyr Gln Leu Thr Lys Ala Pro Ala His Thr Phe Trp 145 150 155 160

Arg Glu Ser Cys Gly Ala Arg Cys Val Leu Pro Trp Ala Glu Phe Glu 165 170 175

Ser Leu Leu Gly Thr Cys His Pro Val Glu Pro Gly Cys Thr Ala Leu 180 185 190

Ala Leu Arg Thr Thr Ile Asp Leu Thr Cys Ser Gly His Val Ser Ile 195 200 205

Phe Glu Phe Asp Val Phe Thr Arg Leu Phe Gln Pro Trp Pro Thr Leu 210 215 220

Leu Lys Asn Trp Gln Leu Leu Ala Val Asn His Pro Gly Tyr Met Ala 225 230 235 240

Phe Leu Thr Tyr Asp Glu Val Gln Glu Arg Leu Gln Ala Cys Arg Asp 245 250 255

Lys Pro Gly Ser Tyr Ile Phe Arg Pro Ser Cys Thr Arg Leu Gly Gln 260 265 270

Trp Ala Ile Gly Tyr Val Ser Ser Asp Gly Ser Ile Leu Gln Thr Ile $\frac{275}{280}$ 285

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Gly Phe Tyr Leu Tyr Pro Asp Gly Lys Thr His Asn Pro Asp Leu Thr 305 310 315 320

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Leu	Leu 370	Cys	Ser	Cys	Суѕ	Leu 375	Ala	Ala	Trp	Gln	His 380	Ser	Asp	Ser ·	Gln	
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360

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Gln Glr	ser 35	Tyr S	er Val	Thr Ty:	Gly	Ile :	Ile	Leu	Asn 45	Arg	Leu	Val		
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Arg Glu Ile Met Glu Asn Arg Tyr Gly Gln Lys Gly Asn Ala Ile Arg 50 55 60

Ile Glu Ile Val Val Tyr Thr Gly Lys Glu Gly Lys Ser Ser His Gly 65 70 75 80

Cys Pro Ile Ala Lys Trp Val Leu Arg Arg Ser Ser Asp Glu Glu Lys 85 90 95

Val Leu Cys Leu Val Arg Gln Arg Thr Gly His His Cys Pro Thr Ala 100 105 110

Val Met Val Val Leu Ile Met Val Trp Asp Gly Ile Pro Leu Pro Met 115 120 125

Ala Asp Arg Leu Tyr Thr Glu Leu Thr Glu Asn Leu Lys Ser Tyr Asn 130 135 140

Gly His Pro Thr Asp Arg Arg Cys Thr Leu Asn Glu Asn Arg Thr Cys 145 150 155 160

Thr Cys Gln Gly Ile Asp Pro Glu Thr Cys Gly Ala Ser Phe Ser Phe 165 170 175

Gly Cys Ser Trp Ser Met Tyr Phe Asn Gly Cys Lys Phe Gly Arg Ser 180 185 190

Pro Ser Pro Arg Arg Phe Arg Ile Asp Pro Ser Ser Pro Leu His Glu
195 200 205

Lys Asn Leu Glu Asp Asn Leu Gln Ser Leu Ala Thr Arg Leu Ala Pro 210 215 220

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- Gly Pro Gly Ile Ser Gln Leu Gly Glu Val Ala Pro Leu Pro Thr Leu 500 505 510
- Ser Ala Pro Val Met Glu Pro Leu Ile Asn Ser Glu Pro Ser Thr Gly 515 520 525
- Val Thr Glu Pro Leu Thr Pro His Gln Pro Asn His Gln Pro Ser Phe 530 535 540
- Leu Thr Ser Pro Gln Asp Leu Ala Ser Ser Pro Met Glu Glu Asp Glu 545 550 555 560
- Gln His Ser Glu Ala Asp Glu Pro Pro Ser Asp Glu Pro Leu Ser Asp 565 570 575
- Asp Pro Leu Ser Pro Ala Glu Glu Lys Leu Pro His Ile Asp Glu Tyr 580 585 590
- Trp Ser Asp Ser Glu His Ile Phe Leu Asp Ala Asn Ile Gly Gly Val 595 600 605
- Ala Ile Ala Pro Ala His Gly Ser Val Leu Ile Glu Cys Ala Arg Arg 610 615 620
- Glu Leu His Ala Thr Thr Pro Val Glu His Pro Asn Arg Asn His Pro 625 630 635 640
- Thr Arg Leu Ser Leu Val Phe Tyr Gln His Lys Asn Leu Asn Lys Pro 645 650 655
- Gln His Gly Phe Glu Leu Asn Lys Ile Lys Phe Glu Ala Lys Glu Ala 660 665 670

Lys Asn Lys Lys Met Lys Ala Ser Glu Gln Lys Asp Gln Ala Asn 675 680 685

Glu Gly Pro Glu Gln Ser Ser Glu Val Asn Glu Leu Asn Gln Ile Pro 690 695 700

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Thr Val Phe Thr Asp His Met Leu Thr Val Glu Trp Ser Ser Glu Phe 50 55 60

Gly Trp Glu Lys Pro His Ile Lys Pro Leu Gln Asn Leu Ser Leu His 65 70 75 80

Pro Gly Ser Ser Ala Leu His Tyr Ala Val Glu Leu Phe Glu Gly Leu 85 90 95

Lys Ala Phe Arg Gly Val Asp Asn Lys Ile Arg Leu Phe Gln Pro Asn 100 105 110

Leu Asn Met Asp Arg Met Tyr Arg Ser Ala Val Arg Ala Thr Leu Pro 115 120 125

Val Phe Asp Lys Glu Glu Leu Leu Glu Cys Ile Gln Gln Leu Val Lys 130 135 140

Leu Asp Gln Glu Trp Val Pro Tyr Ser Thr Ser Ala Ser Leu Tyr Ile 145 150 160

Arg Pro Ala Phe Ile Gly Thr Glu Pro Ser Leu Gly Val Lys Lys Pro 165 170 175

Thr Lys Ala Leu Leu Phe Val Leu Ser Pro Val Gly Pro Tyr Phe 180 185 190

Ser Ser Gly Thr Phe Asn Pro Val Ser Leu Trp Ala Asn Pro Lys Tyr 195 200 205

Val Arg Ala Trp Lys Gly Gly Thr Gly Asp Cys Lys Met Gly Gly Asn 210 215 220

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Gln Gln Val Leu Trp Leu Tyr Gly Arg Asp His Gln Ile Thr Glu Val 245 250 255

Gly Thr Met Asn Leu Phe Leu Tyr Trp Ile Asn Glu Asp Gly Glu Glu 260 265 270

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Asn Arg Val Arg Glu Met Phe Ser Ser Gly Thr Ala Cys Val Val Cys 325 330 335

Pro Val Ser Asp Ile Leu Tyr Lys Gly Glu Thr Ile His Ile Pro Thr 340 345 350

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Trp Phe Gly Pro Trp Gly Val Pro Arg Val Pro Cys Gln Pro Cys Ser 100 105 110

Trp Ala Pro Leu Gly Thr His Gly Cys Asp Glu Trp Gly Arg Arg Ala 115 120 125

Arg Arg Gly Val Glu Val Ala Ala Gly Ala Ser Ser Gly Glu Thr 130 135 140

Arg Gln Pro Gly Asn Gly Thr Arg Ala Gly Gly Pro Glu Glu Thr Ala 145 150 155 160

Ala Gln Tyr Ala Val Ile Ala Ile Val Pro Val Phe Cys Leu Met Gly 165 170 175

Leu Leu Gly Ile Leu Val Cys Asn Leu Leu Lys Arg Lys Gly Tyr His 180 185 190

Cys Thr Ala His Lys Glu Val Gly Pro Gly Pro Gly Gly Gly Gly Ser 195 200 205

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Gly Val Leu Val Arg Leu Ile Thr Glu Lys Lys Glu Asn Ala Ala 225 230 235 240

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Ser His Arg Pro Val Ser Lys Leu Pro Pro Ala Pro Pro Asn Val Pro 260 265 270

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- Gly Ala Ala Leu Gly Gln Ser His Glu Ala Arg Ala Thr Phe Lys Ile
- Thr Ser Gly Val Thr Tyr Asn Pro Asn Leu Gln Asp Lys Leu Ser Val 70 75
- Asp Phe Lys Val Leu Ala Phe Asp Leu Gln Gln Met Ile Asp Glu Ile 95 90 85
- Phe Leu Ser Ser Asn Leu Lys Asn Glu Tyr Lys Asn Ser Arg Val Leu 100
- Gln Phe Glu Asn Gly Ser Ile Ile Val Val Phe Asp Leu Phe Phe Ala
- Gln Trp Val Ser Asp Gln Asn Val Lys Glu Glu Leu Ile Gln Gly Leu 130 135
- Glu Ala Asn Lys Ser Ser Gln Leu Val Thr Phe His Ile Asp Leu Asn 145 150
- Ser Val Asp Ile Leu Asp Lys Leu Thr Thr Thr Ser His Leu Ala Thr 170 175 165
- Pro Gly Asn Val Ser Ile Glu Cys Leu Pro Gly Ser Ser Pro Cys Thr 180 185

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- Thr His Tyr Pro Lys Pro Ser Glu Thr Ser Val Val Cys Gln Trp Ile 245 250 255
- Ile Arg Val Asn Gln Gly Leu Ser Ile Lys Leu Ser Phe Asp Asp Phe 260 265 270
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- Ser Lys Ile Leu Arg Ala Ser Ile Trp Glu Thr Asn Pro Gly Thr Ile 290 295 300
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- Gly Lys Asn Ile Gln Leu His Phe Gln Glu Phe Asp Leu Glu Asn Ile 565 570 575
- Asn Asp Val Val Glu Ile Arg Asp Gly Glu Glu Ala Asp Ser Leu Leu 580 585 590
- Leu Ala Val Tyr Thr Gly Pro Gly Pro Val Lys Asp Val Phe Ser Thr 595 600 605
- Thr Asn Arg Met Thr Val Leu Leu Ile Thr Asn Asp Val Leu Ala Arg 610 615 620
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- Gly Leu Val Arg Phe Arg Ile Gln Ser Ile Trp His Thr Ala Cys Ala 690 695 700
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Asp Lys Glu Arg Phe Trp Gln Arg Cys Leu Arg Leu Ile Gln Arg Leu

295

Ser Pro Gln Met Leu Arg Leu Asn Ala Asp Pro His Phe Phe Thr Gln 315 310 Val Phe Gln Asp Leu Lys Asn Glu Gly Glu Ala Ala Ala Ser Gly Gly 325 330 Gly Pro Pro Ser Gly Gly Ala Pro Ala Ala Ser Ser Ala Ala Arg Asp 345 Ser Cys Ala Ala Gly Thr Lys His Trp Thr Met Asn Leu Asp Arg 360 <210> 270 <211> 513 <212> DNA <213> Homo sapiens <220> <221> misc feature <222> (457)..(457) <223> n = unknown <220> <221> misc_feature <222> (497)..(497) $\langle 223 \rangle$ n = unknown <220> <221> misc_feature <222> (499)..(499) $\langle 223 \rangle$ n = unknown <220> <221> misc_feature <222> (509)..(509) $\langle 223 \rangle$ n = unknown <400> 270 60 ttttattttt ttttttctta aaaaggatac tttaatttat tgacactggg aagcacattg gcaaagaaag tcaatttctt ttacagtatc taatagctat ttctattgcc tgttcaaact 120 agcaaaatgt aacagatgct agattcccta aagtacggcg ctttaggtta catttgcaac 180 aatagcttac atctaaatgt tacattagtt actgaatttg taatcttcac aaatgtgtga 240 atagtcagtt gatcaaaaat aacgatttcc tgctacaaga gaacgcatag cagaaaatgt 300

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<210> 271

<211> 34

<212> PRT

<213> Homo sapiens

<400> 271

Met Leu Asp Ser Leu Lys Tyr Gly Ala Leu Gly Tyr Ile Cys Asn Asn 1 5 10 15

Ser Leu His Leu Asn Val Thr Leu Val Thr Glu Phe Val Ile Phe Thr 20 25 30

Asn Val

<210> 272

<211> 408

<212> DNA

<213> Homo sapiens

<400> 272

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<210> 273

<211> 58

<212> PRT

<213> Homo sapiens

<400> 273

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Ser Thr Glu Ile Leu Leu Lys Ser Asn Phe Met Phe Leu Pro Ser Val 20 25 30

His Phe Phe Val Val Val Val Gly Met Ile Phe Thr Glu Lys Asn 35 40 45

Val Lys His Pro Trp Pro Phe Trp Glu Val 50 55

<210> 274

<211> 1646

<212> DNA

<213> Homo sapiens

<400> 274

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<210> 275 <211> 393 <212> PRT <213> Homo sapiens

<400> 275

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Leu His Phe His Ser Val Thr Phe Trp Val Gly Asn Ala Lys Gln Ala 20 25

Ala Ser Phe Tyr Cys Ser Lys Met Gly Phe Glu Pro Leu Ala Tyr Arg

Gly Leu Glu Thr Gly Ser Arg Glu Val Val Ser His Val Ile Lys Gln 50 55

Gly Lys Ile Val Phe Val Leu Ser Ser Ala Leu Asn Pro Trp Asn Lys

Glu Met Gly Asp His Leu Val Lys His Gly Asp Gly Val Lys Asp Ile

Ala Phe Glu Val Glu Asp Cys Asp Tyr Ile Val Gln Lys Ala Arg Glu 100

Arg Gly Ala Lys Ile Met Arg Glu Pro Trp Val Glu Gln Asp Lys Phe 120 115 Gly Lys Val Lys Phe Ala Val Leu Gln Thr Tyr Gly Asp Thr Thr His Thr Leu Val Glu Lys Met Asn Tyr Ile Gly Gln Phe Leu Pro Gly Tyr Glu Ala Pro Ala Phe Met Asp Pro Leu Leu Pro Lys Leu Pro Lys Cys 170 Ser Leu Glu Met Ile Asp His Ile Val Gly Asn Gln Pro Asp Gln Glu Met Val Ser Ala Ser Glu Trp Tyr Leu Lys Asn Leu Gln Phe His Arg 200 Phe Trp Ser Val Asp Asp Thr Gln Val His Thr Glu Tyr Ser Ser Leu 210 215 220 Arg Ser Ile Val Val Ala Asn Tyr Glu Glu Ser Ile Lys Met Pro Ile Asn Glu Pro Ala Pro Gly Lys Lys Ser Gln Ile Gln Glu Tyr Val 245 250 Asp Tyr Asn Gly Gly Ala Gly Val Gln His Ile Ala Leu Lys Thr Glu Asp Ile Ile Thr Ala Ile Arg His Leu Arg Glu Arg Gly Leu Glu Phe Leu Ser Val Pro Ser Thr Tyr Tyr Lys Gln Leu Arg Glu Lys Leu Lys Thr Ala Lys Ile Lys Val Lys Glu Asn Ile Asp Ala Leu Glu Glu Leu

· 330

Lys Ile Leu Val Asp Tyr Asp Glu Lys Gly Tyr Leu Leu Gln Ile Phe

Thr Lys Pro Val Gln Asp Arg Pro Thr Leu Phe Leu Glu Val Ile Gln 340 345 350

Arg His Asn His Gln Gly Phe Gly Ala Gly Asn Phe Asn Ser Leu Phe 355 360 365

Lys Ala Phe Glu Glu Glu Gln Asn Leu Arg Gly Asn Leu Thr Asn Met 370 380

Glu Thr Asn Gly Val Val Pro Gly Met 385 390

<210> 276 <211> 1913

<212> DNA

<213> Homo sapiens

<400> 276

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Met Ser Gly Arg Gly Ser Gly Asn Gly Arg Ala Ser Ala Pro Arg Leu 5 15

Leu Leu Phe Leu Val Pro Leu Leu Trp Ala Pro Ala Ala Val Arg 20

Ala Gly Pro Asp Glu Asp Leu Ser His Arg Asn Lys Glu Pro Pro Ala 35

Pro Ala Gln Gln Leu Gln Pro Gln Pro Val Ala Val Gln Gly Pro Glu 50

Pro Ala Arg Val Glu Lys Ile Phe Thr Pro Ala Ala Pro Val His Thr 80

<210> 277 <211> 324

<212> PRT

<213> Homo sapiens

<400> 277

Asn Lys Glu Asp Pro Ala Thr Gln Thr Asn Leu Gly Phe Ile His Ala 85 90 95

- Phe Val Ala Ala Ile Ser Val Ile Ile Val Ser Glu Leu Gly Asp Lys
 100 105 110
- Thr Phe Phe Ile Ala Ala Ile Met Ala Met Arg Tyr Asn Arg Leu Thr 115 120 125
- Val Leu Ala Gly Ala Met Leu Ala Leu Gly Leu Met Thr Cys Leu Ser 130 135 140
- Val Leu Phe Gly Tyr Ala Thr Thr Val Ile Pro Arg Val Tyr Thr Tyr 145 150 155 160
- Tyr Val Ser Thr Val Leu Phe Ala Ile Phe Gly Ile Arg Met Leu Arg 165 170 175
- Glu Gly Leu Lys Met Ser Pro Asp Glu Gly Gln Glu Glu Leu Glu Glu 180 185 190
- Val Gln Ala Glu Leu Lys Lys Lys Asp Glu Glu Phe Gln Arg Thr Lys 195 200 205
- Leu Leu Asn Gly Pro Gly Asp Val Glu Thr Gly Thr Ser Ile Thr Val 210 215 220
- Pro Gln Lys Lys Trp Leu His Phe Ile Ser Pro Ile Phe Val Gln Ala 225 230 235 240
- Leu Thr Leu Thr Phe Leu Ala Glu Trp Gly Asp Arg Ser Gln Leu Thr 245 250 255
- Thr Ile Val Leu Ala Ala Arg Glu Asp Pro Tyr Gly Val Ala Val Gly 260 265 270
- Gly Thr Val Gly His Cys Leu Cys Thr Gly Leu Ala Val Ile Gly Gly 275 280 285
- Arg Met Ile Ala Gln Lys Ile Ser Val Arg Thr Val Thr Ile Ile Gly 290 295 300

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Gly Ile Val Phe Leu Ala Phe Ala Phe Ser Ala Leu Phe Ile Ser Pro 305 310 315 320

Asp Ser Gly Phe

<210> 278

<211> 369

<212> DNA

<213> Homo sapiens

<400> 278

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<210> 279

<211> 46

<212> PRT

<213> Homo sapiens

<400> 279

Ile Leu Leu Thr Ser Pro Lys Glu Glu Val Val Ala Phe Pro Lys Arg
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Ser Ser His Gly Gly Asn Glu Ser Val Pro His Lys Pro Thr Val Tyr 20 25 30

Arg Pro His Ile Arg Asn Leu Thr Val Leu Gln Gly Ser Ser 35 40 45

<210> 280

<211> 1601

<212> DNA

<213> Homo sapiens

<400> 280

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tcaaatttgt	ccgaagccgt	gggcagcccg	ctgccggagc	cgcccgagaa	aatggtgccc	360
cgtggttgcc	tgagccctcg	ggccgtccct	ccggccaccc	gggagcgcgg	cgggggaggc	420
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<210> 281 <211> 407 <212> PRT

<213> Homo sapiens

<400> 281

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Gly Thr Leu Val Gly Lys Arg Val Ser Asn Leu Ser Glu Ala Val Gly 20 25 30

Ser Pro Leu Pro Glu Pro Pro Glu Lys Met Val Pro Arg Gly Cys Leu 35 40 45

Ser Pro Arg Ala Val Pro Pro Ala Thr Arg Glu Arg Gly Gly Gly 50 55 60

Pro Glu Glu Glu Pro Val Asp Gly Leu Ala Gly Ser Ala Ala Gly Pro 65 70 75 80

Gly Ala Glu Pro Gln Val Ala Gly Ala Ala Met Leu Gly Pro Gly Pro 85 90 95

Pro Ala Pro Ser Val Asp Ser Leu Ser Gly Gln Gly Gln Pro Ser Ser 100 105 110

Ser Asp Thr Glu Ser Asp Phe Tyr Glu Glu Ile Glu Val Ser Cys Thr 115 120 125

Pro Asp Cys Ala Thr Gly Asn Ala Glu Tyr Gln His Ser Lys Gly Ser 130 135 140

Gly Ser Glu Ala Leu Val Gly Ser Pro Asn Gly Gly Ser Glu Thr Pro 145 150 155 160

Lys Ser Asn Gly Gly Ser Gly Gly Gly Ser Gln Gly Thr Leu Ala 165 170 175

Cys Ser Ala Ser Asp Gln Met Arg Arg Tyr Arg Thr Ala Phe Thr Arg 180 185 190

Glu Gln Ile Ala Arg Leu Glu Lys Glu Phe Tyr Arg Glu Asn Tyr Val 195 200 205 Ser Arg Pro Arg Arg Cys Glu Leu Ala Ala Ala Leu Asn Leu Pro Glu 210 215 220

Thr Thr Ile Lys Val Trp Phe Gln Asn Arg Arg Met Lys Asp Lys Arg 225 230 235 240

Gln Arg Leu Ala Met Thr Trp Pro His Pro Ala Asp Pro Ala Phe Tyr 245 250 255

Thr Tyr Met Met Ser His Ala Ala Ala Ala Gly Gly Leu Pro Tyr Pro 260 265 270

Phe Pro Ser His Leu Pro Leu Pro Tyr Tyr Ser Pro Val Gly Leu Gly 275 280 285

Ala Ala Ser Ala Ala Ser Ala Ala Ala Ser Pro Phe Ser Gly Ser Leu 290 295 300

Arg Pro Leu Asp Thr Phe Arg Val Leu Ser Gln Pro Tyr Pro Arg Pro 305 310 315 320

Glu Leu Leu Cys Ala Phe Arg His Pro Pro Leu Tyr Pro Gly Pro Ala 325 330 335

His Gly Leu Gly Ala Ser Ala Gly Gly Pro Cys Ser Cys Leu Ala Cys 340 345 350

His Ser Gly Pro Ala Asn Gly Leu Ala Pro Arg Ala Ala Ala Ala Ser 355 360 365

Asp Phe Thr Cys Ala Ser Thr Ser Arg Ser Asp Ser Phe Leu Thr Phe 370 375 380

Ala Pro Ser Val Leu Ser Lys Ala Ser Ser Val Ala Leu Asp Gln Arg 385 390 395 400

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<211> 201

<212> DNA

<213> Homo sapiens

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Leu Ser Lys Leu Leu Lys Phe Leu Thr Val Ser Phe Phe Ala Phe Leu 20 25 30	
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cgagatggct tcattgacaa ggaggacctg aaggacacct atgcctccct gggcaagacc	300
aacgtcaagg acgacgagct ggacgccatg ctcaaagagg cctcggggcc catcaacttc	360
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<210> 285

<211> 173

<212> PRT

<213> Homo sapiens

<400> 285

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Gln Glu Phe Lys Glu Ala Phe Thr Leu Met Asp Gln Asn Arg Asp Gly 35 40

Phe Ile Asp Lys Glu Asp Leu Lys Asp Thr Tyr Ala Ser Leu Gly Lys 50 55

Thr Asn Val Lys Asp Asp Glu Leu Asp Ala Met Leu Lys Glu Ala Ser 65 70 75 80

Gly Pro Ile Asn Phe Thr Met Phe Leu Asn Leu Phe Gly Glu Lys Leu 85 90 95

Ser Gly Thr Asp Ala Glu Glu Thr Ile Leu Asn Ala Phe Lys Met Leu 100 105 110

Asp Pro Asp Gly Lys Gly Lys Ile Asn Lys Glu Tyr Ile Lys Arg Leu 115 120 125

Leu Met Ser Gln Ala Asp Lys Met Thr Ala Glu Glu Val Asp Gln Met 130 135 140

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Leu Ser Tyr Val Ile Thr His Gly Glu Glu Lys Glu Glu 165 170

<210> 286

<211> 296

<212> DNA

<213> Homo sapiens

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Tyr Ser Thr Arg Lys Arg Ser Ala Gln Leu Trp Leu Gly Pro Ala Ala 50 55 60

Phe Ile Asn His Asp Cys Lys Pro Asn Cys Lys Phe Val Pro Ala Asp 65 70 75 80

Gly Asn Ala Ala Cys Val Lys Val Leu Arg Asp Ile Glu Pro Gly Asp 85 90 95

Glu Val Thr Cys Phe Tyr Gly Glu Gly Phe Phe Gly Glu Lys Asn Glu 100 105 110

His Cys Glu Cys His Thr Cys Glu Arg Lys Gly Glu Gly Ala Phe Arg 115 120 125

Thr Arg Pro Arg Glu Pro Ala Leu Pro Pro Arg Pro Leu Asp Lys Tyr 130 140

Gln Leu Arg Glu Thr Lys Arg Arg Leu Gln Gln Gly Leu Asp Ser Gly 145 150 155 160

Ser Arg Gln Gly Leu Leu Gly Pro Arg Ala Cys Val His Pro Ser Pro 165 170 175

Leu Arg Arg Asp Pro Phe Cys Ala Ala Cys Gln Pro Leu Arg Leu Pro 180 185 190

Ala Cys Ser Ala Arg Pro Asp Thr Ser Pro Leu Trp Leu Gln Trp Leu 195 200 205

Pro Gln Pro Gln Pro Arg Val Arg Pro Arg Lys Arg Arg Pro Arg 210 215 220

326

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Leu	His	Arg	Trp	Gly 245	Gly	Cys	Gly	Pro	His 250	Cys	Arg	Leu	Arg	Gly 255	Glu	
Ala	Leu	Val	Ala 260	Leu	Gly	Gln	Pro	Pro 265	His	Ala	Arg	Trp	Ala 270	Pro	Gln	
Gln	Asp	Trp 275	His	Trp	Ala	Arg	Arg 280	Tyr	Gly	Leu	Pro	Tyr 285	Val	Val	Arg	
Val	Asp 290	Leu	Arg	Arg	Leu	Ala 295	Pro	Ala	Pro	Pro	Ala 300	Thr	Pro	Ala	Pro	
Ala 305	Gly	Thr	Pro	Gly	Pro 310	Ile	Leu	Ile	Pro	Lys 315	Gln	Ala	Leu	Ala	Phe 320	
Ala	Pro	Phe	Ser	Pro 325	Pro	Lys	Arg	Leu	Arg 330	Leu	Val	Val	Ser	His 335	Ser	
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Gly Gly Pro Cys Leu Xaa Ser Gln Leu His Gly Arg Gln Arg Gln Glu 50 55 60

Asn Arg Leu Asn Pro Gly Gly Xaa Gly Cys Ser Glu Pro Lys Leu Ala 65 70 75 80

Thr Ala Leu Gln Pro Gly Cys Gln Ser Lys Gly Leu Ser Gln Lys Gln 85 90 95

Lys Gln Ser Lys Lys Lys Lys Lys Thr Pro Lys Asn Lys Xaa Xaa 100 105 110

Xaa Ala Gly Cys Gly Gly Ser Arg Leu Ser Ser Gln His Phe Gly Arg 115 120 125

Pro Gly Gly Gln Ile Thr Xaa Gly Gln Glu Phe Glu Thr Ser Leu Ile 130 135 140

Asn Met Val Lys Leu Cys Leu Tyr Xaa Lys Tyr Ile Asn Xaa Pro Gly 145 150 155 160

Met Ala Ala His Ala Cys Asn Pro Ser Tyr Thr Gly Asp Arg Gly Arg 165 170 175

Arg Ile Ala Xaa Thr Gln Glu Val Glu Ala Ala Val Ser Gln Asn Leu

180 185 190 ,

Pro Leu His Ser Ser Arg Gly Val Arg Ala Arg Ala Tyr Leu Lys Asn 195 200 205

Lys Asn Lys Ala Lys Lys Lys Lys Lys Pro Pro Lys Thr Lys Xaa 210 215 220

Xaa Xaa Leu Gly Val Val Ala His Ala Cys His Pro Ser Thr Leu Gly 225 230 235 240

Asp Gln Glu Gly Arg Ser Leu Glu Val Arg Ser Leu Arg Pro Ala Xaa 245 250 255

Ser Thr Trp Xaa Asn Cys Val Ser Ile Lys Asn Thr Xaa Ile Ser Gln 260 265 270

Glu Trp Arg Pro Met Pro Val Ile Pro Ala Thr Arg Glu Thr Glu Ala 275 280 285

Gly Glu Ser Leu Glu Pro Arg Arg Leu Arg Leu Gln Xaa Ala Lys Thr 290 295 300

Cys His Cys Thr Pro Ala Gly Val Ser Glu Gln Gly Pro Ile Ser Lys 305 310 315 320

Thr Lys Thr Lys Gln Lys Lys Lys Lys Asn Pro Gln Lys Gln Xaa 325 330 335

Xaa Xaa Phe Cys Phe Trp Gly Phe Phe Phe Phe Phe Phe Cys Phe Val 340 345 350

Phe Val Phe Glu Ile Gly Pro Cys Ser Asp Thr Pro Ala Gly Val Gln 355 360 365

Trp Gln Val Leu Ala His Cys Ser Leu Asn Leu Leu Gly Ser Ser Asp 370 375 380

Ser Pro Ala Ser Val Ser Arg Val Ala Gly Ile Thr Gly Met Gly Arg 385 390 395 400

His Ser Trp Leu Ile Tyr Val Phe Leu Ile Glu Thr Gln Phe His His

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Trp	Ser	Pro 435	Lys	Val	Leu	Gly	Xaa 440	Gln	Ala	Xaa	Ala	Thr 445	Thr	Pro	Ser
Xaa	Xaa 450	Xaa	Phe	Val	Phe	Gly 455	Gly	Phe	Phe	Phe	Phe 460	Phe	Phe	Ala	Leu
Phe 465	Leu	Phe	Leu	Arg	Xaa 470	Ala	Leu	Ala	Leu	Thr 475	Pro	Arg	Leu	Glu	Cys 480
Ser	Gly	Lys	Phe	Trp 485	Leu	Thr	Ala	Ala	Ser 490	Thr	Ser	Trp	Val	Gln 495	Ala
Ile	Leu	Leu	Pro 500	Leu	Ser	Pro	Val	Xaa 505	Leu	Gly	Leu	Gln	Ala 510	Trp	Ala
Ala	Ile	Pro 515	Gly	Xaa	Phe	Met	Tyr 520	Phe	Xaa	Xaa	Arg	His 525	Ser	Phe	Thr
Met	Leu 530	Ile	Arg	Leu	Val	Ser 535	Asn	Ser	Xaa	Pro	Gln 540	Val	Ile	Суѕ	Pro
Pro 545	Gly	Leu	Pro	Lys	Cys 550	Trp	Asp	Asp	Arg	Arg 555	Glu	Pro	Pro	His	Pro 560
Ala	Xaa	Xaa	Xaa	Leu 565	Phe	Leu	Gly	Val	Phe 570	Phe	Phe	Phe	Phe	Leu 575	Leu ·
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Ala	Val	Ala 595	Ser	Phe	Gly	Ser	Leu 600	Gln	Pro	Gln	Pro	Pro 605	Gly	Phe	Lys
Arg	Phe 610	Ser	Cys	Leu	Суз	Leu 615	Pro	Cys	Ser	Trp	Asp 620	Tyr	Arg	His	Gly

Pro Pro Phe Leu Ala Asn Leu Cys Ile Phe Asn Arg Asp Thr Val Ser

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Leu Gly Ala Ala Leu Lys Ala Thr Gly Lys Asn Leu Ser Glu Ala Gln 35. 40 45

Leu Arg Lys Leu Ile Ser Glu Val Asp Ser Asp Gly Asp Gly Glu Ile 50 55 60

Ser Phe Gln Glu Phe Leu Thr Ala Ala Arg Lys Ala Arg Ala Gly Leu 65 70 75 80

Glu Asp Leu Gln Val Ala Phe Arg Ala Phe Asp Gln Asp Gly Asp Gly 85 90 95

His Ile Thr Val Asp Glu Leu Arg Arg Ala Met Ala Gly Leu Gly Gln Pro Leu Pro Gln Glu Glu Leu Asp Ala Met Ile Arg Glu Ala Asp Val Asp Gln Asp Gly Arg Val Asn Tyr Glu Glu Phe Ala Arg Met Leu Ala 135 Gln Glu 145 <210> 296 <211> 154 <212> DNA <213> Homo sapiens <400> 296 60 gagatacacg agaaatccaa attaggatag aattccagaa gaagggagta gcatgtgcaa 120 aaaaaaaaa aaaaaaaaa aaaagtcgta tcga 154 <210> 297 <211> 29 <212> PRT <213> Homo sapiens <400> 297 Arg Glu Asp Asp Arg Arg Ala Thr Phe Glu Leu Ile Leu Lys Lys 5 10 15 Lys Lys Ile Glu Ile His Glu Lys Ser Lys Leu Gly 25 <210> 298 <211> 452 <212> DNA <213> Homo sapiens <220> <221> misc_feature <222> (1)..(452) $\langle 223 \rangle$ n = unknown

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Leu Ile Leu Tyr Phe Phe Leu Val Glu Met Glu Phe Leu His Val Gly 55

Gln Ala Gly Leu Glu Leu Pro Thr Ser Asp Asp Pro Ser Val Ser Ala

Ser Gln Ser Ala Arg Tyr Arg Thr Gly His His Ala Arg Leu Cys Leu

Ala Asn Phe Cys Gly Arg Asn Arg Val Ser Leu Met Cys Pro Ser Trp 105

Ser Pro Glu Leu Lys Gln Ser Thr Cys Leu Ser Leu Pro Lys Cys Trp 120

Asp Tyr Arg Arg Ala Ala Val Pro Gly Leu Phe Ile Leu Phe Phe Leu 130 135 140

Arg His Arg Cys Pro Thr Leu Thr Gln Asp Glu Val Gln Trp Cys Asp 145 150 155 160

His Ser Ser Leu Gln Pro Ser Thr Pro Glu Ile Lys His Pro Pro Ala 165 170 175

Ser Ala Ser Gln Val Ala Gly Thr Lys Asp Met His His Tyr Thr Trp 180 185 190

Leu Ile Phe Ile Phe Ile Phe Asn Phe Leu Arg Gln Ser Leu Asn Ser 195 200 205

Val Thr Gln Ala Gly Val Gln Trp Arg Asn Leu Gly Ser Leu Gln Pro 210 215 220

Leu Pro Pro Gly Phe Lys Leu Phe Ser Cys Pro Ser Leu Leu Ser Ser 225 230 235 240

Trp Asp Tyr Arg Arg Pro Pro Arg Leu Ala Asn Phe Phe Val Phe Leu 245 250 255

Val Glu Met Gly Phe Thr Met Phe Ala Arg Leu Ile Leu Ile Ser Gly 260 265 270

Pro Cys Asp Leu Pro Ala Ser Ala Ser Gln Ser Ala Gly Ile Thr Gly 275 280 285

Val Ser His His Ala Arg Leu Ile Phe Asn Phe Cys Leu Phe Glu Met 290 295 300

Glu Ser His Ser Val Thr Gln Ala Gly Val Gln Trp Pro Asn Leu Gly 305 310 315 320

Ser Leu Gln Pro Leu Pro Pro Gly Leu Lys Arg Phe Ser Cys Leu Ser 325 330 335

Leu Pro Ser Ser Trp Asp Tyr Gly His Leu Pro Pro His Pro Ala Asn 340 345 350

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Ser Gln Thr Pro Asp Leu Arg 370 375

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<211> 56

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Asn Ile Leu Thr Leu Met Tyr Ala Cys Leu Ser Leu Asn Ser Thr Ser 35 40 45

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Phe Phe Leu Asp Glu Asp Ser Tyr Thr Pro Thr Val Ser Ser Ser Lys 50 55 60

Ile Thr Ile 65

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3840

3892

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- <211> 220
- <213> Homo sapiens

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Asp Gln Leu Glu Ile Gln Leu Thr Glu Gln Leu Arg Ser Leu Ile Pro 35 40 45

Asn Glu Asp Val Arg Lys Phe Met Ser His Val Ile Trp Thr Leu Lys 50 55 60

Met Glu Cys Ser Glu Thr His Val Gln Gly Ser Cys Ala Lys Leu Met 65 70 75 80

Ser Arg Thr Gly Leu Leu Met Lys Leu Leu Ser Glu Gln Glu Ala 85 90 95

Lys Ala Leu Asn Val Glu Trp Asp Thr Asp Gln Gln Lys Thr Asn Tyr 100 105 110

Ile Asn Glu Asn Met Glu Gln Asn Glu Gln Lys Glu Gln Lys Ser Ser 115 120 125

Glu Leu Met Lys Glu Val Pro Gly Tyr Asp Tyr Lys Asn Lys Leu Ile 130 135 140

Phe Ala Ile Ser Val Thr Val Ile Leu Ile Ile Leu Ile Ile Ile Phe 145 150 155 160

Cys Phe Ile Glu Val Lys Thr Ile Ile Asn Ser Gly Phe Gln Asn Thr 165 170 175

Ile Leu Cys Leu Cys Gly Phe Arg Ile His Lys Leu Lys Thr Asn Val 180 185 190

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Pro Pro Arg Pro Pro Lys Val Leu Gly Leu Ile Thr Gly Val Ser His 40

Tyr Ala Gln Pro Pro Trp Ser Tyr Phe Tyr Leu Lys His Ile His Tyr

Asn Ser Ile Asp Leu Ile Thr Lys Val Pro Ile Leu Leu Lys Cys Phe

Ile Val Ile Lys Ile Gln Lys Leu Leu Met Leu Ala Asn Lys Ile Gln 90

Ala Lys His Lys Cys Val Lys 100

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<211> 2985

<212> DNA

<213> Homo sapiens

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<211> 474

<212> PRT

<213> Homo sapiens

<400> 311

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Met Leu Glu Asn Tyr Arg Asn Leu Val Ser Leu Gly Val Ala Ile Ser 35 40 45

Asn Pro Asp Leu Val Thr Cys Leu Glu Gln Arg Lys Glu Pro Tyr Asn 50 55 60

Val Lys Ile His Lys Ile Val Ala Arg Pro Pro Ala Met Cys Ser His 65 70 75 80

Phe Thr Gln Asp His Trp Pro Val Gln Gly Ile Glu Asp Ser Phe His 85 90 95

Lys Leu Ile Leu Arg Arg Tyr Glu Lys Cys Gly His Asp Asn Leu Gln
100 105 110

Leu Arg Lys Gly Cys Lys Ser Leu Asn Glu Cys Lys Leu Gln Lys Gly
115 120 125

Gly Tyr Asn Glu Phe Asn Glu Cys Leu Ser Thr Thr Gln Ser Lys Ile 130 135 140

Leu Gln Cys Lys Ala Ser Val Lys Val Val Ser Lys Phe Ser Asn Ser 145 150 155 160

Asn Lys Arg Lys Thr Arg His Thr Gly Glu Lys His Phe Lys Glu Cys 165 170 175

Gly Lys Ser Phe Gln Lys Phe Ser His Leu Thr Gln His Lys Val Ile 180 185 190

His Ala Gly Glu Lys Pro Tyr Thr Cys Glu Glu Cys Gly Lys Ala Phe 195 200 205

Lys Trp Ser Leu Ile Phe Asn Glu His Lys Arg Ile His Thr Gly Glu 210 215 220

Lys Pro Phe Thr Cys Glu Glu Cys Gly Ser Ile Phe Thr Thr Ser Ser 225 230 235 240

His Phe Ala Lys His Lys Ile Ile His Thr Gly Glu Lys Pro Tyr Lys 245 250 255

Cys Glu Glu Cys Gly Lys Ala Phe Asn Arg Phe Thr Thr Leu Thr Lys 260 265 270

His Lys Arg Ile His Ala Gly Glu Lys Pro Ile Thr Cys Glu Glu Cys 275 280 285

Arg Lys Ile Phe Thr Ser Ser Ser Asn Phe Ala Lys His Lys Arg Ile 290 295 300

His Thr Gly Glu Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Ala Phe 305 310 315 320

Asn Arg Ser Thr Thr Leu Thr Lys His Lys Arg Ile His Thr Gly Glu 325 330 335

Lys Pro Tyr Thr Cys Glu Glu Cys Gly Lys Ala Phe Arg Gln Ser Ser 340 345 350

Lys Leu Asn Glu His Lys Lys Val His Thr Gly Glu Arg Pro Tyr Lys 355 360 365

Cys Asp Glu Cys Gly Lys Ala Phe Gly Arg Ser Arg Val Leu Asn Glu 370 375 380

His Lys Lys Ile His Thr Gly Glu Lys Pro Tyr Lys Cys Glu Glu Cys 385 390 395 400

Gly Lys Ala Phe Arg Arg Ser Thr Asp Arg Ser Gln His Lys Lys Ile 405 410 415

His Ser Ala Asp Lys Pro Tyr Lys Cys Lys Glu Cys Asp Lys Ala Phe 420 425 430

Lys Gln Phe Ser Leu Leu Ser Gln His Lys Lys Ile His Thr Val Asp 435 440 445

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His Leu Asn Lys His Lys Lys Ile His Thr 465

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<211> 540

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gccagt																18	0
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<212> PRT <213> Homo sapiens

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Ala Ser Pro His Leu Ser Val Thr Arg His Met Val Gln Ala Gly Leu

20 25 30

Gln Gln Asn Phe Pro Gln Leu Gln His Ser Gln Cys Leu Ala Leu Asp $35 \hspace{1cm} 40 \hspace{1cm} 45$

Phe Gln Phe His Leu Val Glu Leu Gly His Gly Thr Lys Asp Arg Asn 50 55 60

Lys 65

<210> 316 <211> 468 <212> DNA

<213> Homo sapiens

<400> 316

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<211> 49

<212> PRT

<213> Homo sapiens

<400> 317

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Ile Asn Leu Gly Ser Ser Arg Ser Arg Leu Thr Ala Ser Arg Pro
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Val Ala Glu Cys Thr Pro Ala Leu Gly Asn Val Trp Ala Ala Ser Cys $35 \hspace{1cm} 40 \hspace{1cm} 45$

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<400> 319

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Phe

<210> 320

<211> 449

<212> DNA

<213> Homo sapiens

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<211> 235

<212> PRT

<213> Homo sapiens

<400> 321

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Lys Pro Thr Glu Asn Leu Gly Asn Thr Thr Leu Thr Thr Glu Thr Ile 50 55 60

Lys Ala Pro Val Lys Ser Thr Glu Asn Pro Glu Lys Thr Ala Ala Val 65 70 75 80

Thr Lys Thr Ile Lys Pro Ser Val Lys Val Thr Gly Asp Lys Ser Leu 85 90 95

Thr Thr Thr Ser Ser His Leu Asn Lys Thr Glu Val Thr His Gln Val 100 105 110

Pro Thr Gly Ser Phe Thr Leu Ile Thr Ser Arg Thr Lys Leu Ser Ser 115 120 125

Ile Thr Ser Glu Ala Thr Gly Asn Glu Ser His Pro Tyr Leu Asn Lys 130 135 140

Asp Gly Ser Gln Lys Gly Ile His Ala Gly Gln Met Gly Glu Asn Asp Ser Phe Pro Ala Trp Ala Ile Val Ile Val Val Leu Val Ala Val Ile 165 170 Leu Leu Val Phe Leu Gly Leu Ile Phe Leu Val Ser Tyr Met Met 185 Arg Thr Arg Arg Thr Leu Thr Gln Asn Thr Gln Tyr Asn Asp Ala Glu Asp Glu Gly Gly Pro Asn Ser Tyr Pro Val Tyr Leu Met Glu Gln Gln Asn Leu Gly Met Gly Gln Ile Pro Ser Pro Arg 230 <210> 322 <211> 419 <212> DNA <213> Homo sapiens <400> 322 60 ttccctcaca ctccctctcc tcaaacaaac atttcgggat tcactggcac ttgcaggttg 120 ttaggaaccg gtcttgattt tataagacac ctttcaaaac ataatcccgg tgcggcgtgt 180 aaggtgtggg aaccgtttag tcacagacac cgtcccgtct acctcccccg agtccagcct 240 cctgagagat gctctccgcc taagaccgct aacagctcaa ttgggtctca ttgatcccac 300 360 tcaccatcta gagccctgtt gcctcattaa tccgttgtgc caccagctca cgggctgcaa 419 ctgggaagag acqaqacctq tttatccatc gccgacactg ggatacgcag caatctgca <210> 323 <211> 97 <212> PRT <213> Homo sapiens <400> 323 Phe Pro His Thr Pro Ser Pro Gln Thr Asn Ile Ser Gly Phe Thr Gly 1 5 10

Thr Cys Arg Leu Leu Gly Thr Gly Leu Asp Phe Ile Arg His Leu Ser 20 25 30

Lys His Asn Pro Gly Ala Ala Cys Lys Val Trp Glu Pro Phe Ser His 35 40 45

Arg His Arg Pro Val Tyr Leu Pro Arg Val Gln Pro Trp Val Gly Ala 50 55 60

Ala Gln Arg Leu Ala Ala Leu Gly Leu Leu Ala Val Pro Ser Phe Pro 65 70 75 80

Pro Glu Arg Cys Ser Pro Pro Lys Thr Ala Asn Ser Ser Ile Gly Ser 85 90 95

His

<210> 324

<211> 573

<212> DNA

<213> Homo sapiens

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<400> 325

Met Lys Pro Tyr Asn Thr Ile Glu Lys Phe Leu Gly Lys Ala Ile Gly 1 5 10 15

His Leu Arg Ile Leu Pro Thr Ile Ser Met His Leu Phe Tyr Arg Glu 20 25 30

Ser Arg Gly Leu Tyr Trp Thr Glu Phe Ser Gly 35 40

<210> 326 <211> 2351 <212> DNA

<213> Homo sapiens

<400> 326

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<210> 327 <211> 97 <212> PRT <213> Homo sapiens

<400> 327

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ggegetgeat tegageggtg gggeteetgt cegtgegett teeteeegea geeeeggeeg 120
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<210> 329

<211> 79

<212> PRT

<213> Homo sapiens

<400> 329

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Pro Ala Ala Gly Arg Cys Ile Arg Ala Val Gly Leu Leu Ser Val Arg 20 25 30

Arg Ser Pro Leu Phe Pro Asn Arg Cys Ser Phe Ser Gly Ala Leu Ser 50 60

Arg His Gly Leu Thr Pro Leu Gln Ser Tyr Leu Arg Ser Val Leu 65 70 75

<210> 330 <211> 1618

<212> DNA

<213> Homo sapiens

<400> 330

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<210> 331

<211> 43

<212> PRT

<213> Homo sapiens

<400> 331

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Ala Ala Gly Ala Arg Arg Thr Ala Ala Ser Ala Ala Gln Arg Thr Cys 20 25 30

Pro Ala Ala Gly Pro Gly Pro His Arg Gly Arg 35 40

<210> 332

<211> 3673

<212> DNA

<213> Homo sapiens

<400> 332

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<210> 333

<211> 1165

<212> PRT

<213> Homo sapiens

<400> 333

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His Pro Gly Arg Pro Ala Ala Ser Leu Ser Pro Gly Leu Gly Ala Val $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$

Leu Gly Val Ala Gly Arg Gln Val Ala Asp Pro Arg Phe Arg Arg Asp 35 40 45

Trp Phe Arg Ile Pro Ser Pro Pro Ala Glu Ser Ala Gly Pro Ala Arg 50 55 60

Gln Ala Gly Phe Ala Ala Ala Pro Pro Ala Arg Ala Gly Pro Ala Leu 65 70 75 80

Ser Thr Met Lys Gly Thr Arg Ala Ile Gly Ser Val Pro Glu Arg Ser 85 90 95

Pro Ala Gly Val Asp Leu Ser Leu Thr Gly Leu Pro Pro Pro Val Ser 100 105 110

Arg Arg Pro Gly Ser Ala Ala Thr Thr Lys Pro Ile Val Arg Ser Val 115 120 125

Ser Val Val Thr Gly Ser Glu Gln Lys Arg Lys Val Leu Glu Ala Thr 130 135 140

Gly Pro Gly Gly Ser Gln Ala Ile Asn Asn Leu Arg Arg Ser Asn Ser 145 150 155 160

Thr Thr Gln Val Ser Gln Pro Arg Ser Gly Ser Pro Arg Pro Thr Glu 165 170 175

Pro Thr Asp Phe Leu Met Leu Phe Glu Gly Ser Pro Ser Gly Lys Lys 180 . 185 190

- Arg Pro Ala Ser Leu Ser Thr Ala Pro Ser Glu Lys Gly Ala Thr Trp
 195 200 205
- Asn Val Leu Asp Asp Gln Pro Arg Gly Phe Thr Leu Pro Ser Asn Ala 210 215 220
- Arg Ser Ser Ser Ala Leu Asp Ser Pro Ala Gly Pro Arg Arg Lys Glu 225 230 235 240
- Cys Thr Val Ala Leu Ala Pro Asn Phe Thr Ala Asn Asn Arg Ser Asn 245 250 255
- Lys Gly Ala Val Gly Asn Cys Val Thr Thr Met Val His Asn Arg Tyr 260 265 270
- Thr Pro Ser Glu Arg Ala Pro Pro Leu Lys Ser Ser Asn Gln Thr Ala 275 280 285
- Pro Ser Leu Asn Asn Ile Ile Lys Ala Ala Thr Cys Glu Gly Ser Glu 290 295 300
- Ser Ser Gly Phe Gly Lys Leu Pro Lys Asn Val Ser Ser Ala Thr His 305 310 315 320
- Ser Ala Arg Asn Asn Thr Gly Gly Ser Thr Gly Leu Pro Arg Arg Lys 325 330 335
- Glu Val Thr Glu Glu Glu Ala Glu Arg Phe Île His Gl
n Val As
n Gl
n 340 $345 \qquad \qquad 350$
- Ala Ala Val Thr Ile Gln Arg Trp Tyr Arg His Gln Val Gln Arg Arg 355 360 365
- Gly Ala Gly Ala Ala Arg Leu Glu His Leu Leu Gln Ala Lys Arg Glu 370 375 380
- Glu Gln Arg Gln Arg Ser Gly Glu Gly Thr Leu Leu Asp Leu His Gln 385 390 395 400

Gln Lys Glu Ala Arg Arg Lys Ala Arg Glu Glu Lys Ala Arg Gln 405 410 415

- Ala Arg Arg Ala Ala Ile Gln Glu Leu Gln Gln Lys Arg Ala Leu Arg
 420 425 430
- Ala Gln Lys Ala Ser Thr Ala Glu Arg Gly Pro Pro Glu Asn Pro Arg
 435
 440
 445
- Glu Thr Arg Val Pro Gly Met Arg Gln Pro Ala Gln Glu Leu Ser Pro 450 455 460
- Thr Pro Gly Gly Thr Ala His Gln Ala Leu Lys Ala Asn Asn Ala Gly 465 470 475 480
- Gly Gly Leu Pro Ala Ala Gly Pro Gly Asp Arg Cys Leu Pro Thr Ser 485 490 495
- Asp Ser Ser Pro Glu Pro Gln Gln Pro Pro Glu Asp Arg Thr Gln Asp 500 505 510
- Val Leu Ala Gln Asp Ala Ala Gly Asp Asn Leu Glu Met Met Ala Pro 515 520 525
- Ser Arg Gly Ser Ala Lys Ser Arg Gly Pro Leu Glu Glu Leu Leu His 530 540
- Thr Leu Gln Leu Leu Glu Lys Glu Pro Asp Ala Leu Pro Arg Pro Arg 545 550 555
- Thr His His Arg Gly Arg Tyr Ala Trp Ala Ser Glu Val Thr Thr Glu 565 570 575
- Asp Asp Ala Ser Ser Leu Thr Ala Asp Asn Leu Glu Lys Phe Gly Lys 580 585
- Leu Ser Ala Phe Pro Glu Pro Pro Glu Asp Gly Thr Leu Leu Ser Glu 595 600
- Ala Lys Leu Gln Ser Ile Met Ser Phe Leu Asp Glu Met Glu Lys Ser 610 615 620

Gly Gln Asp Gln Leu Asp Ser Gln Gln Glu Gly Trp Val Pro Glu Ala 625 630 635 640

- Gly Pro Gly Pro Leu Glu Leu Gly Ser Glu Val Ser Thr Ser Val Met 645 650 655
- Arg Leu Lys Leu Glu Val Glu Glu Lys Lys Gln Ala Met Leu Leu 660 665 670
- Gln Arg Ala Leu Ala Gln Gln Arg Asp Leu Thr Ala Arg Arg Val Lys 675 680 685
- Glu Thr Glu Lys Ala Leu Ser Arg Gln Leu Gln Arg Gln Arg Glu His 690 695 700
- Tyr Glu Ala Thr Ile Gln Arg His Leu Ala Phe Ile Asp Gln Leu Ile 705 710 715 720
- Glu Asp Lys Lys Val Leu Ser Glu Lys Cys Glu Ala Val Val Ala Glu
 725 730 735
- Leu Lys Gln Glu Asp Gln Arg Cys Thr Glu Arg Val Ala Gln Ala Gln 740 745 750
- Ala Gln His Glu Leu Glu Ile Lys Lys Leu Lys Glu Leu Met Ser Ala 755 760 765
- Thr Glu Lys Ala Arg Arg Glu Lys Trp Ile Ser Glu Lys Thr Lys Lys
 770 775 780
- Ile Lys Glu Val Thr Val Arg Gly Leu Glu Pro Glu Ile Gln Lys Leu 785 790 795 800
- Ile Ala Arg His Lys Gln Glu Val Arg Arg Leu Lys Ser Leu His Glu 805 810 815
- Ala Glu Leu Gln Ser Asp Glu Arg Ala Ser Gln Arg Cys Leu Arg 820 825 830
- Gln Ala Glu Glu Leu Arg Glu Gln Leu Glu Arg Glu Lys Glu Ala Leu 835 840 845

Gly Gln Gln Glu Arg Glu Arg Ala Arg Gln Arg Phe Gln Gln His Leu 850 855 860

- Glu Gln Glu Gln Trp Ala Leu Gln Gln Gln Arg Gln Arg Leu Tyr Ser 865 870 875 880
- Glu Val Ala Glu Glu Arg Glu Arg Leu Gly Gln Gln Ala Ala Arg Gln 885 890 895
- Arg Ala Glu Leu Glu Glu Leu Arg Gln Gln Leu Glu Glu Ser Ser Ser 900 905 910
- Ala Leu Thr Arg Ala Leu Arg Ala Glu Phe Glu Lys Gly Arg Glu Glu 915 920 925
- Gln Glu Arg Arg His Gln Met Glu Leu Asn Thr Leu Lys Gln Gln Leu 930 940
- Glu Leu Glu Arg Gln Ala Trp Glu Ala Gly Arg Thr Arg Lys Glu Glu 945 950 955 960
- Ala Trp Leu Leu Asn Arg Glu Glu Glu Leu Arg Glu Glu Ile Arg Lys 965 970 975
- Gly Arg Asp Lys Glu Ile Glu Leu Val Ile His Arg Leu Glu Ala Asp 980 985 990
- Met Ala Leu Ala Lys Glu Glu Ser Glu Lys Ala Ala Glu Ser Arg Ile 995 1000 1005
- Lys Arg Leu Arg Asp Lys Tyr Glu Ala Glu Leu Ser Glu Leu Glu 1010 1015 1020
- Gln Ser Glu Arg Lys Leu Gln Glu Arg Cys Ser Glu Leu Lys Gly 1025 1030 1035
- Gln Leu Gly Glu Ala Glu Gly Glu Asn Leu Arg Leu Gln Gly Leu 1040 1045 1050
- Val Arg Gln Lys Glu Arg Ala Leu Glu Asp Ala Gln Ala Val Asn 1055 1060 1065

Glu Gln Leu Ser Ser Glu Arg Ser Asn Leu Ala Gln Val Ile Arg 1070 1075 1080

- Gln Glu Phe Glu Asp Arg Leu Ala Ala Ser Glu Glu Glu Thr Arg 1085 1090 1095
- Gln Ala Lys Ala Glu Leu Ala Thr Leu Gln Ala Arg Gln Gln Leu 1100 1105 1110
- Glu Leu Glu Glu Val His Arg Arg Val Lys Thr Ala Leu Ala Arg 1115 1120 1125
- Lys Glu Glu Ala Val Ser Ser Leu Arg Thr Gln His Glu Ala Ala 1130 1135 1140
- Val Lys Arg Ala Asp His Leu Glu Glu Leu Leu Glu Gln His Arg 1145 1150 1155
- Arg Pro Thr Pro Ser Thr Lys 1160 1165

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<211> 1183

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<213> Homo sapiens

<400> 334

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<211> 169

<212> PRT

<213> Homo sapiens

<400> 335

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Gln Val Trp Thr Leu Gln Gly Gln Asn Leu Val Ala Val Pro Arg Ser 35 40 45

Asp Ser Val Thr Pro Val Thr Val Ala Val.Ile Thr Cys Lys Tyr Pro 50 55 60

Glu Ala Leu Glu Gln Gly Arg Gly Asp Pro Ile Tyr Leu Gly Ile Gln 65 70 75 80

Asn Pro Glu Met Cys Leu Tyr Cys Glu Lys Val Gly Glu Gln Pro Thr 85 90 95

Leu Gln Leu Lys Glu Gln Lys Ile Met Asp Leu Tyr Gly Gln Pro Glu 100 105 110

Pro Val Lys Pro Phe Leu Phe Tyr Arg Ala Lys Thr Gly Arg Thr Ser 115 120 125

Thr Leu Glu Ser Val Ala Phe Pro Asp Trp Phe Ile Ala Ser Ser Lys 130 135 Arg Asp Gln Pro Ile Ile Leu Thr Ser Glu Leu Gly Lys Ser Tyr Asn 145 150 155 Thr Ala Phe Glu Leu Asn Ile Asn Asp 165 <210> 336 <211> 129 <212> DNA <213> Homo sapiens <400> 336 60 tatacqqctq cqaqaaqacq acagaaqgga tacacaacca gatatttcca ggaaggaaag 120 129 aagtcgtat <210> 337 <211> 42 <212> PRT <213> Homo sapiens <400> 337 Tyr Gly Cys Glu Lys Thr Thr Glu Gly Ile His Asn Gln Ile Phe Pro 5 Gly Arg Lys Val Glu Ser Pro Ala Asn Arg Tyr Ser Leu Lys Gly Asp Lys Lys Lys Lys Lys Lys Lys Val Val <210> 338 <211> 694 <212> DNA <213> Homo sapiens <400> 338 60 qqaqaqqccq qqctqqccaq aqtcttcqqc ctccqqcqtc qqqaaatqqc qqcqqqqqq gggatggagt gacggttcct tggatatcac ccagagtatt gaagacgacc cacttctgga 120 tgcccagctt ctcccacacc actcattaca agctcacttt agaccccgat tccatcctct 180

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<211> 127

<212> PRT

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20 25 30

Arg Asn Arg Gly Tyr Asn Leu Ile Tyr Arg Ser Thr Arg His Leu Lys 35 40 45

Arg Leu Ala Leu Met Ile Gln Ser Ser Gly Asn Thr Val Leu Leu Leu 50 55 60 .

Ile Leu Cys Met Gln His Ser Phe Pro Glu Pro Gly Arg Leu Tyr Leu 65 70 75 80

Asp Leu Ile Leu Ala Ile Leu Ala Leu Glu Leu Ile Cys Ser Leu Ile 85 90 95

Cys Leu Leu Ile Tyr Thr Val Lys Ile Arg Arg Phe Asn Lys Ala Lys 100 105 110

Pro Glu Pro Asp Ile Leu Asp Glu Asp Asn Ile Tyr Ala Tyr Pro 115 120 125

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340

2974

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<400> 341

Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln 1 5 10 15

Arg Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr 20 25 30

Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly 35 40 45

Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly 50 55 60

Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile 65 70 75 80

Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser 85 90 95

Gly Arg Glu Ile Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Ile 100 105 110

Ile Gln Asn Asp Thr Gly Phe Tyr Thr Leu His Val Ile Lys Ser Asp 115 120 125

Leu Val Asn Glu Glu Ala Thr Gly Gln Phe Arg Val Tyr Pro Glu Leu 130 135 140

Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro Val Glu Asp Lys 145 150 155 160

Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Ala Thr Tyr 165 170 175

Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln 180 185 190

Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn Val Thr Arg Asn 195 200 . 205

Asp Thr Ala Ser Tyr Lys Cys Glu Thr Gln Asn Pro Val Ser Ala Arg 210 215 220

Arg Ser Asp Ser Val Ile Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro 225 230 235 240

Thr Ile Ser Pro Leu Asn Thr Ser Tyr Arg Ser Gly Glu Asn Leu Asn 245 250 255

Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe 260 265 270

Val Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn 275 280 285

Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys Gln Ala His Asn Ser 290 295 300

Asp Thr Gly Leu Asn Arg Thr Thr Val Thr Thr Ile Thr Val Tyr Ala 305 310 315 320

Glu Pro Pro Lys Pro Phe Ile Thr Ser Asn Asn Ser Asn Pro Val Glu 325 330 335

Asp Glu Asp Ala Val Ala Leu Thr Cys Glu Pro Glu Ile Gln Asn Thr 340 345 350

Thr Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Pro Val Ser Pro Arg 355 360 365

Leu Gln Leu Ser Asn Asp Asn Arg Thr Leu Thr Leu Leu Ser Val Thr 370 375 380

Arg Asn Asp Val Gly Pro Tyr Glu Cys Gly Ile Gln Asn Glu Leu Ser 385 390 395 400

Val Asp His Ser Asp Pro Val Ile Leu Asn Val Leu Tyr Gly Pro Asp 405 410 415

Asp Pro Thr Ile Ser Pro Ser Tyr Thr Tyr Tyr Arg Pro Gly Val Asn 420 425 430

Leu Ser Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser 435 440 445

Trp Leu Ile Asp Gly Asn Ile Gln Gln His Thr Gln Glu Leu Phe Ile 450 455 460

Ser Asn Ile Thr Glu Lys Asn Ser Gly Leu Tyr Thr Cys Gln Ala Asn 465 470 475 480

Asn Ser Ala Ser Gly His Ser Arg Thr Thr Val Lys Thr Ile Thr Val 485 490 495

Ser Ala Glu Leu Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Lys Pro 500 505 510

Val Glu Asp Lys Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Ala Gln 515 520 525

Asn Thr Thr Tyr Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser 530 540

Pro Arg Leu Gln Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Phe Asn 545 550 550 560

Val Thr Arg Asn Asp Ala Arg Ala Tyr Val Cys Gly Ile Gln Asn Ser 565 570 575

Val Ser Ala Asn Arg Ser Asp Pro Val Thr Leu Asp Val Leu Tyr Gly
580 585 590

Pro Asp Thr Pro Ile Ile Ser Pro Pro Asp Ser Ser Tyr Leu Ser Gly 595 600 605

Ala Asn Leu Asn Leu Ser Cys His Ser Ala Ser Asn Pro Ser Pro Gln 610 615 620

Tyr Ser Trp Arg Ile Asn Gly Ile Pro Gln Gln His Thr Gln Val Leu 625 630 635 640

Phe Ile Ala Lys Ile Thr Pro Asn Asn Gly Thr Tyr Ala Cys Phe 645 650 655

Val Ser Asn Leu Ala Thr Gly Arg Asn Asn Ser Ile Val Lys Ser Ile 660 665 670

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Thr Val Ser Ala Ser Gly Thr Ser Pro Gly Leu Ser Ala Gly Ala Thr

Val Gly Ile Met Ile Gly Val Leu Val Gly Val Ala Leu Ile 695

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<211> 832

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<213> Homo sapiens

<220>

<221> misc_feature

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<210> 343

<211> 33

<212> PRT

<213> Homo sapiens

<400> 343

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Val Lys Ser Gly Phe Pro Ala Cys His Gly Lys Leu Leu Ala Thr Trp
20 25 30

Glu

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Leu Leu Pro Leu Arg Glu Gly Val Asp Gly Ala Arg Asp Leu Glu Arg 20 25 30

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Gly Arg Asn Arg Asp Arg Lys Glu Ser Gln Asp Thr Gly Thr Arg Thr 40

Pro Arg Arg Thr Arg Arg Val Ser Glu Leu Leu

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<213> Homo sapiens

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n Glu Ala Val Gly Val Cys Ser Tyr Gly 1 5 10 15

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Ala Leu Phe Asp Gln Phe Arg Glu Trp Pro Asp Gly Tyr Val Arg Phe

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Cys Leu Gly Val Val Cys Thr Gln Ala Cys Thr Leu Pro Asp Gly 85 90 95

Ser Arg Leu Gln Leu Arg Pro Ala Ile Cys Asp Lys Ala Arg Leu Lys $100 \hspace{1.5cm} 105 \hspace{1.5cm} 110$

Gln Gln Lys Lys Ala Cys Pro Asn Cys His Ser Ala Leu Glu Leu Ile 115 120 125

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Asp Gly Asn Ala Ile Phe Phe Gln Ala Lys Gly Val His Asp His Pro 145 150 155 160

Arg Pro Glu Ser Lys Ser Glu Thr Glu Ala Arg Arg Ser Ala Ile Lys 165 170 175

Arg Gln Met Ala Ser Phe Tyr Gln Pro Gln Lys Lys Arg Ile Arg Glu 180 185 190

Ser Glu Ala Glu Glu Asn Gln Asp Ser Ser Gly His Phe Ser Asn Ile 195 200 205

Pro Pro Leu Glu Asn Pro Glu Asp Phe Asp Ile Val Thr Glu Thr Ser 210 215 220

Phe Pro Ile Pro Gly Gln Pro Cys Pro Ser Phe Pro Lys Ser Asp Val 225 230 235 240

Tyr Lys Ala Thr Cys Asp Leu Ala Thr Phe Gln Gly Asp Lys Met Pro 245 250 255

Pro Phe Gln Lys Tyr Ser Ser Pro Arg Ile Tyr Leu Pro Arg Pro Pro 260 265 270

Cys Ser Tyr Glu Leu Ala Asn Pro Gly Tyr Thr Asn Ser Ser Pro Tyr 275 280 285

- Pro Thr Leu Tyr Lys Asp Ser Thr Ser Ile Pro Asn Asp Thr Asp Trp 290 295 300
- Val His Leu Asn Thr Leu Gln Cys Asn Val Asn Ser Tyr Ser Ser Tyr 305 310 315 320
- Glu Arg Ser Phe Asp Phe Thr Asn Lys Gln His Gly Trp Lys Pro Ala 325 330 335
- Leu Gly Lys Pro Ser Leu Val Glu Arg Thr Asn His Gly Gln Phe Gln 340 345 350
- Ala Met Ala Thr Arg Pro Tyr Tyr Asn Pro Glu Leu Pro Cys Arg Tyr 355 360 365
- Leu Thr Thr Pro Pro Pro Gly Ala Pro Ala Leu Gln Thr Val Ile Thr 370 375 380
- Thr Thr Thr Lys Val Ser Tyr Gln Ala Tyr Gln Pro Pro Ala Met Lys 385 390 395 400
- Tyr Ser Asp Ser Val Arg Glu Val Lys Ser Leu Ser Ser Cys Asn Tyr 405 410 415
- Ala Pro Glu Asp Thr Gly Met Ser Val Tyr Pro Glu Pro Trp Gly Pro 420 425 430
- Pro Val Thr Val Thr Arg Ala Ala Ser Pro Ser Gly Pro Pro Pro Met 435 440 445
- Lys Ile Ala Gly Asp Cys Arg Ala Ile Arg Pro Thr Val Ala Ile Pro 450 455 460
- His Glu Pro Val Ser Ser Arg Thr Asp Glu Ala Glu Thr Trp Asp Val 465 470 475 480
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1860

1875

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Arg Asp Thr Ser Asp Thr Pro Leu Cys Gln Leu Ser Gln Gly Ile Tyr 85 90 95

Leu Thr Asn Arg Tyr Met Ser Ile Ser Leu Val Thr Ala Ile Ala Val 100 105 110

Asp Arg Tyr Val Ala Val Arg His Pro Leu Arg Ala Arg Gly Leu Arg 115 120 125

Ser Pro Arg Gln Ala Ala Ala Val Cys Ala Val Leu Trp Val Leu Val 130 · 135 140

Ile Gly Ser Leu Val Ala Arg Trp Leu Leu Gly Ile Gln Glu Gly Gly 145 150 155 160

Phe Cys Phe Arg Ser Thr Arg His Asn Phe Asn Ser Met Ala Phe Pro 165 170 175

Leu Leu Gly Phe Tyr Leu Pro Leu Ala Val Val Phe Cys Ser Leu 185 Lys Val Val Thr Ala Leu Ala Gln Arg Pro Pro Thr Asp Val Gly Gln 200 Ala Glu Ala Thr Arg Lys Ala Ala Arg Met Val Trp Ala Asn Leu Leu 215 Val Phe Val Val Cys Phe Leu Pro Leu His Val Gly Leu Thr Val Arg 230 Leu Ala Val Gly Trp Asn Ala Cys Ala Leu Leu Glu Thr Ile Arg Arg 245 Ala Leu Tyr Ile Thr Ser Lys Leu Ser Asp Ala Asn Cys Cys Leu Asp 265 Ala Ile Cys Tyr Tyr Met Ala Lys Glu Phe Gln Glu Ala Ser Ala 275 280 Leu Ala Val Ala Pro Ser Ala Lys Ala His Lys Ser Gln Asp Ser Leu 300 . 295 Cys Val Thr Leu Ala 305 <210> 352 <211> 1803 <212> DNA <213> Homo sapiens <400> 352 60 atgacagogg ctccggcqtc tccqcagcaq atcagggacc ggctgctgca ggccatcgac 120 ccccagagca acatccggaa catggtggcg gtgctggaag tcatctccag cctggagaaa 180 taccctatta ccaaagaggc acttgaggaa acacgacttg ggaagctcat caacgacgtc cgcaagaaaa ccaagaacga ggagctcgcc aagcgggcca agaagctgct gcggagctgg 240 300 cagaagctca tegageegge acaccageat gaggeggege tgeggggget ggegggggee 360 accggctctg ccaacggggg cgcacacaac tgccggccgg aggtgggggc ggctggccca 420 cccaggagca tccatgacct gaagagccgc aatgacctcc agaggctgcc cgggcagcgg

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<213> Homo sapiens

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- Glu Val Ile Ser Ser Leu Glu Lys Tyr Pro Ile Thr Lys Glu Ala Leu $35 \hspace{1.5cm} 40 \hspace{1.5cm} 45$
- Glu Glu Thr Arg Leu Gly Lys Leu Ile Asn Asp Val Arg Lys Lys Thr 50 55 60
- Lys Asn Glu Glu Leu Ala Lys Arg Ala Lys Lys Leu Leu Arg Ser Trp 65 70 75 80
- Gln Lys Leu Ile Glu Pro Ala His Gln His Glu Ala Ala Leu Arg Gly 85 90 95
- Leu Ala Gly Ala Thr Gly Ser Ala Asn Gly Gly Ala His Asn Cys Arg 100 105 110
- Pro Glu Val Gly Ala Ala Gly Pro Pro Arg Ser Ile His Asp Leu Lys 115 120 125
- Ser Arg Asn Asp Leu Gln Arg Leu Pro Gly Gln Arg Leu Asp Arg Leu 130 140
- Gly Ser Arg Lys Arg Gly Asp Gln Arg Asp Phe Gly His Pro Gly 145 150 150
- Pro Pro Pro Lys Val Ser Lys Ala Ser His Asp Pro Leu Val Pro Asn 165 170 175
- Ser Ser Pro Leu Pro Thr Asn Gly Ile Ser Gly Ser Pro Glu Ser Phe 180 185 190
- Ala Ser Ser Leu Asp Gly Ser Gly His Ala Gly Pro Glu Gly Ser Arg 195 200 205
- Leu Glu Arg Asp Glu Asn Asp Lys His Ser Gly Lys Ile Pro Val Asn 210 215 220

Ala Val Arg Pro His Thr Ser Ser Pro Gly Leu Gly Lys Pro Pro Gly Pro Cys Leu Gln Pro Lys Ala Ser Val Leu Gln Gln Leu Asp Arg Val Asp Glu Thr Pro Gly Pro Pro His Pro Lys Gly Pro Pro Arg Cys Ser Phe Ser Pro Arg Asn Ser Arg His Glu Gly Ser Phe Ala Arg Gln Gln Ser Leu Tyr Ala Pro Lys Gly Ser Val Pro Ser Pro Ser Pro Arg Pro Gln Ala Leu Asp Ala Thr Gln Val Pro Ser Pro Leu Pro Leu Ala Gln Pro Ser Thr Pro Pro Val Arg Arg Leu Glu Leu Leu Pro Ser Ala Glu Ser Pro Val Cys Trp Leu Glu Gln Pro Glu Ser His Gln Arg Leu Ala Gly Pro Gly Cys Lys Ala Gly Leu Ser Pro Ala Glu Pro Leu Leu Ser Arg Ala Gly Phe Ser Pro Asp Ser Ser Lys Ala Asp Ser Asp Ala Ala Ser Ser Gly Gly Ser Asp Ser Lys Lys Lys Arg Tyr Arg Pro Arg Asp Tyr Thr Val Asn Leu Asp Gly Gln Val Ala Glu Ala Gly Val Lys Pro Val Arg Leu Lys Glu Arg Lys Leu Thr Phe Asp Pro Met Thr Arg Gln Ile Lys Pro Leu Thr Gln Lys Glu Pro Val Arg Ala Asp Ser Pro

Val His Met Glu Gln Gln Ser Arg Thr Glu Leu Asp Lys Gln Glu Ala 450 Lys Ala Ser Leu Gln Ser Pro Phe Glu Gln Thr Asn Trp Lys Glu Leu 470 475 480 465 Ser Arg Asn Glu Ile Ile Gln Ser Tyr Leu Ser Arg Gln Ser Ser Leu 495 490 485 Leu Ser Ser Ser Gly Ala Gln Thr Pro Gly Ala His His Phe Met Ser 505 500 Glu Tyr Leu Lys Gln Glu Glu Ser Thr Arg Gln Gly Ala Arg Gln Leu 515 His Val Leu Val Pro Gln Ser Pro Pro Thr Asp Leu Pro Gly Leu Thr 540 530 Arg Glu Val Thr Gln Asp Asp Leu Asp Arg Ile Gln Ala Ser Gln Trp 560 555 545 550 Pro Gly Val Asn Gly Cys Gln Asp Thr Gln Gly Asn Trp Tyr Asp Trp 565 Thr Gln Cys Ile Ser Leu Asp Pro His Gly Asp Asp Gly Arg Leu Asn 580 585 Ile Leu Pro Tyr Val Cys Leu Asp 595 <210> 354 <211> 1279 <212> DNA <213> Homo sapiens <400> 354 tccaaaaccc gaggtctcgc taaaatcatc atggattcac ttggcgccgt cagcactcga 60 cttgggtttg atctttcaa agagctgaag aaaacaaatg atggcaacat cttctttcc 120 cctgtgggca tcttgactgc aattggcatg gtcctcctgg ggacccgagg agccaccgct 180 240 tcccagttgg aggaggtgtt tcactctgaa aaagagacga agagctcaag aataaaggct gaagaaaaag aggtgattga gaacacagaa gcagtacatc aacaattcca aaagtttttg 300

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Gly Ile Leu Thr Ala Ile Gly Met Val Leu Leu Gly Thr Arg Gly Ala 35 40 45

Thr Ala Ser Gln Leu Glu Glu Val Phe His Ser Glu Lys Glu Thr Lys 50 55 60

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Thr Tyr Leu Phe Leu Gln Lys Tyr Leu Asp Tyr Val Glu Lys Tyr Tyr 115 120 125

His Ala Ser Leu Glu Pro Val Asp Phe Val Asn Ala Ala Asp Glu Ser 130 135 140

Arg Lys Lys Ile Asn Ser Trp Val Glu Ser Lys Thr Asn Glu Lys Ile 145 150 155 160

Lys Asp Leu Phe Pro Asp Gly Ser Ile Ser Ser Ser Thr Lys Leu Val 165 170 175

Leu Val Asn Met Val Tyr Phe Lys Gly Gln Trp Asp Arg Glu Phe Lys 180 185 190

Lys Glu Asn Thr Lys Glu Glu Lys Phe Trp Met Asn Lys Ser Thr Ser 195 200 205

Lys Ser Val Gln Met Met Thr Gln Ser His Ser Phe Ser Phe Thr Phe 210 215 220

Leu Glu Asp Leu Gln Ala Lys Ile Leu Gly Ile Pro Tyr Lys Asn Asn 225 230 235 240

Asp Leu Ser Met Phe Val Leu Leu Pro Asn Asp Ile Asp Gly Leu Glu 245 250 255

Lys Ile Ile Asp Lys Ile Ser Pro Glu Lys Leu Val Glu Trp Thr Ser 260 265 270

Pro Gly His Met Glu Glu Arg Lys Val Asn Leu His Leu Pro Arg Phe 275 280 285

Glu	Val 290	Glu	Asp	Ser	Tyr	Asp 295	Leu	Giu	Ala	Val	16u 300	Ala	Ala	Met	GIÀ	
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Ala	Val	Thr	Glu 340	Glu	Gly	Thr	Glu	Ala 345	Aļa	Ala	Ala	Thr	Gly 350	Ile	Gly	
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Asn Phe Ser Phe Gly Tyr Ala Leu Val Tyr Thr Ser Pro Val Ile Pro 55

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- Ala His Gly Leu Trp Met Leu Leu Leu Gly Arg Thr Leu Thr Gly Phe 130 135 140
- Ala Gly Gly Leu Thr Ala Ala Cys Ile Pro Val Tyr Val Ser Glu Ile 145 150 155 160
- Ala Pro Pro Gly Val Arg Gly Ala Leu Gly Ala Thr Pro Gln Leu Met 165 170 175
- Ala Val Phe Gly Ser Leu Ser Leu Tyr Ala Leu Gly Leu Leu Pro 180 185 190
- Trp Arg Trp Leu Ala Val Ala Gly Glu Ala Pro Val Leu Ile Met Ile 195 200 205
- Leu Leu Ser Phe Met Pro Asn Ser Pro Arg Phe Leu Ser Arg 210 215 220
- Gly Arg Asp Glu Glu Ala Leu Arg Ala Leu Ala Trp Leu Arg Gly Thr 225 230 235 240
- Asp Val Asp Val His Trp Glu Phe Glu Gln Ile Gln Asp Asn Val Arg 245 250 255
- Arg Gln Ser Ser Arg Val Ser Trp Ala Glu Ala Arg Ala Pro His Val 260 265 270
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Gly Arg Lys Val Leu Leu Phe Val Ser Ala Ala Ile Met Phe Ala Ala 340 345 350

Asn Leu Thr Leu Gly Leu Tyr Ile His Phe Gly Pro Arg Pro Leu Ser 355 360 365

Pro Asn Ser Thr Ala Gly Leu Glu Ser Glu Ser Trp Gly Asp Leu Ala 370 375 380

Gln Pro Leu Ala Ala Pro Ala Gly Tyr Leu Thr Leu Val Pro Leu Leu 385 390 395 400

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Val His Pro Asp Thr Gly Ile Ser Ser Lys Ala Met Gly Ile Met Asn 50 60

Ser Phe Val Asn Asp Ile Phe Glu Arg Ile Ala Gly Glu Ala Ser Arg 65 70 75 80

Leu Ala His Tyr Asn Lys Arg Ser Thr Ile Thr Ser Arg Glu Ile Gln 85 90 95

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Glu Ser Ser Phe Met Ile Cys Leu Pro Ala Cys Leu Leu Phe Val His

Gly Asn Ala Ser Tyr Phe Cys Thr Leu Ile Leu Tyr Pro Glu Ile Leu

Leu Leu Leu Ile Thr Leu Arg Ser Phe Gly Pro Glu Thr Met Arg

Phe Ser Arg Cys Arg Ile Arg Ser Ser Ala Asn Lys Asp Asn Leu Thr 105

Ser Ser Leu Ser Ile Arg Ile Leu Phe Ile Ser Ser Ser Gly Leu Ile 120

Phe Leu Ala Lys Ala Ser Asp Thr Ile Leu Asn Gly Ser Gly Glu Arg

Gly His Ser Phe Leu Val Pro Val Phe Arg Trp Asn Val Ser Ser Phe

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Asn Glu Ile Gln Asn Gly Asn Ala Ser Leu Phe Phe Arg Arg Val Ser 100 105 110

Leu Leu Asp Glu Gly Ile Tyr Thr Cys Tyr Val Gly Thr Ala Ile Gln 115 120 125

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Thr Pro Ile Ser Glu Asn Asn Met Glu Glu Thr Gly Ser Leu Asp Ser 180 185 190

Phe Ser Ile Asn Ser Pro Leu Asn Ile Thr Gly Ser Asn Ser Ser Tyr 195 200 205

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Lys Val Thr Trp Ser Arg Met Lys Ser Gly Thr Phe Ser Val Leu Ala 260 265 270

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WO 02/103028	PC1/1B02/04

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Lys Arg Ile Ile Thr Ile Gln Tyr Gln Lys Met Pro Ile Phe Leu Asp 35 40 45

Glu Glu Glu Gln Arg His Leu Gln Ala Leu Glu Arg Glu Ala Glu Glu 50 55 60

Leu Phe Gln Gln Leu Gln Asp Ser Gln Val Arg Met Thr Gln His Leu 65 70 75 80

Glu Arg Met Lys Asp Met Tyr Arg Glu Leu Trp Glu Thr Cys His Met 85 90 95

Pro Asp Val Val Leu Leu Gln Asp Val Arg Asn Val Ser Ala Arg Thr 100 105 110

Asp Leu Ala Gln Met Gln Lys Pro Gln Pro Val Asn Pro Glu Leu Thr 115 120 125

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Asp Ser Ala Leu Ser Thr Glu Met Ile Pro Cys Tyr Ile Ser Leu Ser 145 150 155 160

Glu Asp Val Arg Tyr Val Ile Phe Gly Asp Asp His Leu Ser Ala Pro 165 170 175

Thr Asp Pro Gln Gly Val Asp Ser Phe Ala Val Trp Gly Ala Gln Ala 180 185 190

Phe Thr Ser Gly Lys His Tyr Trp Glu Val Asp Val Thr Leu Ser Ser 195 200 205

Asn Trp Ile Leu Gly Val Cys Gln Asp Ser Arg Thr Ala Asp Ala Asn 210 215 220

Phe Val Ile Asp Ser Asp Glu Arg Phe Phe Leu Ile Ser Ser Lys Arg 225 230 235 240

Ser Asn His Tyr Ser Leu Ser Thr Asn Ser Pro Pro Leu Ile Gln Tyr 245 250 255

Val Gln Arg Pro Leu Gly Arg Val Gly Val Phe Leu Asp Tyr Asp Asn 260 265 270

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Ile Gln Arg Ile Ser Gln Ala Thr Ala Gln Ile Lys Asn Leu Met Ser 35 40 45

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Gln Leu Gln His Ser Thr Asn Gln Leu Ala Lys Glu Thr Asn Glu Leu 65 70 75 80

Leu Lys Glu Leu Gly Ser Leu Pro Leu Pro Leu Ser Thr Ser Glu Gln 85 90 95

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Phe Ser Ile Glu Asp Val Gln Lys Glu Ile Lys Arg Gly Thr Lys Leu 65 70 75 80

Met Cys Ser Leu Cys His Cys Pro Gly Ala Thr Ile Gly Cys Asp Val 85 90 95

Lys Thr Cys His Arg Thr Tyr His Tyr His Cys Ala Leu His Asp Lys 100 105 110

Ala Gln Ile Arg Glu Lys Pro Ser Gln Gly Ile Tyr Met Ala Tyr Cys 115 120 125

Arg Lys His Lys Lys Thr Ala His Asn Ser Glu Ala Ala Asp Leu Glu 130 135 140

Glu Ser Phe Asn Glu His Glu Leu Glu Pro Ser Ser Pro Lys Ser Lys 145 150 155 160

Lys Lys Ser Arg Lys Gly Arg Pro Arg Lys Thr Asn Phe Lys Gly Leu 165 170 175

Ser Glu Asp Thr Arg Ser Thr Ser Ser His Gly Thr Asp Glu Met Glu 180 185 190

Ser Ser Ser Tyr Arg Asp Arg Ser Pro His Arg Ser Ser Pro Ser Asp

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Tyr Lys Cys Met Leu Phe Ser Ser Gly Thr Val Gln Leu Thr Thr 245 250

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Ile Lys Arg Gly Lys Arg Met Val Cys Ser Phe Tyr Ile Cys Tyr Ala 275 280

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Val	Pro	Gly 35	His	Phe	Gly	Glu	Lys 40	Leu	Ala	Met	Thr	Tyr 45	Gly	Ala	Leu		
Phe	Cys 50	Glu	Thr	Ser	Ala	Lys 55	Asp	Gly	Ser	Asn	Ile 60	Val	Glu	Ala	Val		
Leu 65	His	Leu	Ala	Arg	Glu 70	Val	Lys	Lys	Arg	Thr 75	Asp	Lys	Asp	Asp	Ser 80		
Arg	Ser	Ile	Thr	Asn 85	Leu	Thr	Gly	Thr	Asn 90	Ser	Lys	Lys	Ser	Pro 95	Gln		
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Arg Val Pro Ala Gln Ser Gly Pro Leu Pro Lys Pro Ser Leu Gln Ala

Leu Pro Ser Ser Leu Val Pro Leu Glu Lys Pro Val Thr Leu Arg Cys 35 40 45

Gln Gly Pro Pro Gly Val Asp Leu Tyr Arg Leu Glu Lys Leu Ser Ser

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<213> Homo sapiens

Ser Leu Ala Gly Arg Tyr Arg Cys Ser Tyr Gln Asn Gly Ser Leu Trp 85 90 95

- Ser Leu Pro Ser Asp Gln Leu Glu Leu Val Ala Thr Gly Val Phe Ala 100 105 110
- Lys Pro Ser Leu Ser Ala Gln Pro Gly Pro Ala Val Ser Ser Gly Gly 115 120 125
- Asp Val Thr Leu Gln Cys Gln Thr Arg Tyr Gly Phe Asp Gln Phe Ala 130 135 140
- Leu Tyr Lys Glu Gly Asp Pro Ala Pro Tyr Lys Asn Pro Glu Arg Trp 145 150 155 160
- Tyr Arg Ala Ser Phe Pro Ile Ile Thr Val Thr Ala Ala His Ser Gly 165 170 175
- Thr Tyr Arg Cys Tyr Ser Phe Ser Ser Arg Asp Pro Tyr Leu Trp Ser 180 185 190
- Ala Pro Ser Asp Pro Leu Glu Leu Val Val Thr Gly Thr Ser Val Thr 195 200 205
- Pro Ser Arg Leu Pro Thr Glu Pro Pro Ser Ser Val Ala Glu Phe Ser 210 215 220
- Glu Ala Thr Ala Glu Leu Thr Val Ser Phe Thr Asn Lys Val Phe Thr 225 230 235 240
- Thr Glu Thr Ser Arg Ser Ile Thr Thr Ser Pro Lys Glu Ser Asp Ser 245 250 255
- Pro Ala Gly Pro Ala Arg Gln Tyr Tyr Thr Lys Gly Asn Leu Val Arg 260 265 270
- Ile Cys Leu Gly Ala Val Ile Leu Ile Ile Leu Ala Gly Phe Leu Ala 275 ' 280 285
- Glu Asp Trp His Ser Arg Arg Lys Arg Leu Arg His Arg Gly Arg Ala 290 295 300

Val Gln Arg Pro Leu Pro Pro Leu Pro Pro Leu Pro Gln Thr Arg Lys 305 310 315 320

Ser His Gly Gly Gln Asp Gly Gly Arg Gln Asp Val His Ser Arg Gly 325 330 335

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<213> Homo sapiens

<400> 388

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<211> 258

<212> PRT

<213> Homo sapiens

<400> 389

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Arg Leu Ala Arg Asp Gly Ala His Val Val Ile Ser Ser Arg Lys Gln 35 40 45

Gln Asn Val Asp Arg Ala Met Ala Lys Leu Gln Gly Glu Gly Leu Ser 50 55 60

Val Ala Gly Ile Val Cys His Val Gly Lys Ala Glu Asp Arg Glu Gln 65 70 75 80

Leu Val Ala Lys Ala Leu Glu His Cys Gly Gly Val Asp Phe Leu Val 85 90 95

Cys Ser Ala Gly Val Asn Pro Leu Val Gly Ser Thr Leu Gly Thr Ser 100 105 110

Glu Gln Ile Trp Asp Lys Ile Leu Ser Val Asn Val Lys Ser Pro Ala 115 120 125

Leu Leu Ser Gln Leu Leu Pro Tyr Met Glu Asn Arg Arg Gly Ala 130 135 140

Val Ile Leu Val Ser Ser Ile Ala Ala Tyr Asn Pro Val Val Ala Leu 145 150 155 160

Gly Val Tyr Asn Val Ser Lys Thr Ala Leu Leu Gly Leu Thr Arg Thr 165 170 175

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<210> 391 <211> 63 <212> PRT

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605

<213> Homo sapiens

<400> 391

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Met Ser Gln Arg Thr Gln Ser Ala Ser Gly Phe Leu Arg Asn Lys Glu 35 40 45

Glu Arg Val Pro Lys Leu Leu Pro Arg Ile Tyr Ile Glu Thr Ala 50 55 60

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<211> 297

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<210> 393

<211> 51

<212> PRT

<213> Homo sapiens

<400> 393

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720

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						240
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tgctaccgct						300
acttggcctt						360
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Leu Glu Arg Ala Ala Leu Gly Phe Arg Lys Gly Gly Ser Gly Met Phe

Ala Ser Gly Trp Asn Gln Thr Val Pro Ile Glu Glu Ala Gly Ser Met

Ala Ala Leu Leu Leu Pro Leu Leu Leu Leu Pro Leu Leu Leu 55

<210> 397 <211> 730 <212> PRT

<213> Homo sapiens

<400> 397

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- Ala Leu Ala Ala Ala Ala Asp Pro Glu Gly Pro Glu Gly Gly Cys 100 105 110
- Ser Leu Ala Trp Arg Leu Ala Glu Leu Ala Gln Gln Arg Ala Ala His 115 120 125
- Thr Phe Leu Ile His Gly Ser Arg Phe Ser Tyr Ser Glu Ala Glu 130 135 140
- Arg Glu Ser Asn Arg Ala Ala Arg Ala Phe Leu Arg Ala Leu Gly Trp 145 150 155 . 160
- Asp Trp Gly Pro Asp Gly Gly Asp Ser Gly Glu Gly Ser Ala Gly Glu 165 170 175
- Gly Glu Arg Ala Ala Pro Gly Ala Gly Asp Ala Ala Ala Gly Ser Gly
 180 185 190
- Ala Glu Phe Ala Gly Gly Asp Gly Ala Ala Arg Gly Gly Gly Ala Ala 195 200 205
- Ala Pro Leu Ser Pro Gly Ala Thr Val Ala Leu Leu Leu Pro Ala Gly 210 215 220
- Pro Glu Phe Leu Trp Leu Trp Phe Gly Leu Ala Lys Ala Gly Leu Arg 225 230 235 240
- Thr Ala Phe Val Pro Thr Ala Leu Arg Arg Gly Pro Leu Leu His Cys 245 250 255
- Leu Arg Ser Cys Gly Ala Arg Ala Leu Val Leu Ala Pro Glu Phe Leu 260 265 270
- Glu Ser Leu Glu Pro Asp Leu Pro Ala Leu Arg Ala Met Gly Leu His 275 280 285

Leu Trp Ala Ala Gly Pro Gly Thr His Pro Ala Gly Ile Ser Asp Leu 290 295 300

- Leu Ala Glu Val Ser Ala Glu Val Asp Gly Pro Val Pro Gly Tyr Leu 305 310 315 320
- Ser Ser Pro Gln Ser Ile Thr Asp Thr Cys Leu Tyr Ile Phe Thr Ser 325 330 335
- Gly Thr Thr Gly Leu Pro Lys Ala Ala Arg Ile Ser His Leu Lys Ile 340 345 350
- Leu Gln Cys Gln Gly Phe Tyr Gln Leu Cys Gly Val His Gln Glu Asp 355 360 365
- Val Ile Tyr Leu Ala Leu Pro Leu Tyr His Met Ser Gly Ser Leu Leu 370 375 380
- Gly Ile Val Gly Cys Met Gly Ile Gly Ala Thr Val Val Leu Lys Ser 385 390 395 400
- Lys Phe Ser Ala Gly Gln Phe Trp Glu Asp Cys Gln Gln His Arg Val 405 410 415
- Thr Val Phe Gln Tyr Ile Gly Glu Leu Cys Arg Tyr Leu Val Asn Gln
 420 425 430
- Pro Pro Ser Lys Ala Glu Arg Gly His Lys Val Arg Leu Ala Val Gly 435 440 445
- Ser Gly Leu Arg Pro Asp Thr Trp Glu Arg Phe Val Arg Arg Phe Gly 450 455 460
- Pro Leu Gln Val Leu Glu Thr Tyr Gly Leu Thr Glu Gly Asn Val Ala 465 470 475 480
- Thr Ile Asn Tyr Thr Gly Gln Arg Gly Ala Val Gly Arg Ala Ser Trp 485 490 495
- Leu Tyr Lys His Ile Phe Pro Phe Ser Leu Ile Arg Tyr Asp Val Thr 500 505 510

Thr Gly Glu Pro Ile Arg Asp Pro Gln Gly His Cys Met Ala Thr Ser 515 520 525

- Pro Gly Glu Pro Gly Leu Leu Val Ala Pro Val Ser Gln Gln Ser Pro 530 540
- Phe Leu Gly Tyr Ala Gly Gly Pro Glu Leu Ala Gln Gly Lys Leu 545 550 560
- Lys Asp Val Phe Arg Pro Gly Asp Val Phe Phe Asn Thr Gly Asp Leu 565 570 575
- Leu Val Cys Asp Asp Gln Gly Phe Leu Arg Phe His Asp Arg Thr Gly 580 585 590
- Asp Thr Phe Arg Trp Lys Gly Glu Asn Val Ala Thr Thr Glu Val Ala 595 600 605
- Glu Val Phe Glu Ala Leu Asp Phe Leu Gln Glu Val Asn Val Tyr Gly 610 615 620
- Val Thr Val Pro Gly His Glu Gly Arg Ala Gly Met Ala Ala Leu Val 625 630 635 640
- Leu Arg Pro Pro His Ala Leu Asp Leu Met Gln Leu Tyr Thr His Val 645 650 655
- Ser Glu Asn Leu Pro Pro Tyr Ala Arg Pro Arg Phe Leu Arg Leu Gln 660 665 670
- Glu Ser Leu Ala Thr Thr Glu Thr Phe Lys Gln Gln Lys Val Arg Met 675 680 685
- Ala Asn Glu Gly Phe Asp Pro Ser Thr Leu Ser Asp Pro Leu Tyr Val 690 695 700
- Leu Asp Gln Ala Val Gly Ala Tyr Leu Pro Leu Thr Thr Ala Arg Tyr 705 710 715 720
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Asp Arg Ser Leu Glu Asp Gly Leu Asn Arg Glu Leu Arg Glu Glu Leu 35 40 45

Gly Glu Ala Ala Ala Phe Arg Val Glu Arg Thr Asp Tyr Arg Ser 50 55 60

Ser His Val Gly Ser Gly Pro Arg Val Val Ala His Phe Tyr Ala Lys 65 70 75 80

Arg Leu Thr Leu Glu Glu Leu Leu Ala Val Glu Ala Gly Ala Thr Arg 85 90 95

Ala Lys Asp His Gly Leu Glu Val Leu Gly Leu Val Arg Val Pro Leu
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Tyr Thr Leu Arg Asp Gly Val Gly Gly Leu Pro Thr Phe Leu Glu Asn 115 120 125

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Ala Ala Thr Met Arg Glu Arg Arg Arg Leu Ser Lys Val Asn Glu Ala 115 120 125

Phe Glu Thr Leu Lys Arg Cys Thr Ser Ser Asn Pro Asn Gln Arg Leu 130 135 140

Pro Lys Val Glu Ile Leu Arg Asn Ala Ile Arg Tyr Ile Glu Gly Leu 145 150 155 160

Gln Ala Leu Leu Arg Asp Gln Asp Ala Ala Pro Pro Gly Ala Ala Ala 165 170 175

Ala Phe Tyr Ala Pro Gly Pro Leu Pro Pro Gly Arg Gly Glu His 180 185 190

Tyr Ser Gly Asp Ser Asp Ala Ser Ser Pro Arg Ser Asn Cys Ser Asp 195 200 205

Gly Met Met Asp Tyr Ser Gly Pro Pro Ser Gly Ala Arg Arg Arg Asn 210 215 220

Cys Tyr Glu Gly Ala Tyr Tyr Asn Glu Ala Pro Ser Glu Pro Arg Pro 225 230 235 240

Gly Lys Ser Ala Ala Val Ser Ser Leu Asp Cys Leu Ser Ser Ile Val 245 250 255

Glu Arg Ile Ser Thr Glu Ser Pro Ala Ala Pro Ala Leu Leu Ala 260 265 270

Asp Val Pro Ser Glu Ser Pro Pro Arg Arg Gln Glu Ala Ala Pro 275 280 285

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Phe Glu Ser Pro His Ser Tyr Ile Cys Ser Pro Val Thr Phe Gln Phe 50 55 60

- Phe Tyr Ala Gln Ser Val Lys His Val Asn Val Thr Ile Asp Cys Leu 70 75 80
- Pro Glu Gly Ala Ala Thr Arg Gly Thr Ala Arg Thr Ser Lys Pro Thr 85 90 95
- Thr Lys Ser Gln Lys Thr Leu Pro Ser Thr Ser Pro Gly His Trp Thr 100 105 110
- Gln Ser Thr Pro Trp Ala Ser Ala Leu Arg Ser Ser Pro Trp Thr Glu 115 120 125
- Thr Ala Ala Pro Ser Glu Thr Glu Glu Thr Leu Asn Thr Gly Arg Pro 130 135 140
- Pro Glu Leu Pro Ala Arg Ala Thr Ala Thr Trp Phe Ser Ala Ser His 145 150 155 160
- Thr Leu Pro Ala Leu Ala Thr Arg Arg Val Ala Arg Thr Gln Trp Leu 165 170 175
- Thr Ala Asp Arg Gln Thr Trp Ala Ser Ile Ser Ser Val Pro Trp Ala
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- Gln Thr Ile Ser Glu Lys Lys Pro Gly Gly Ser Leu Trp Glu Thr Arg 195 200 205
- Ser Ser Pro Pro Thr Thr Ala Gly Thr Glu Glu Ala Met Asn Thr Thr 210 220
- Ser Leu Leu Ala Pro Ala Ala Glu Ile Met Ala Thr Pro Gly Ser Pro 225 230 235 240
- Ser Gln Ala Ser Pro Thr Ser Gly Ala Phe Thr His Gly Thr Gln Thr 245 250 255
- Pro Ser Pro Thr Lys Ala Thr Ala Pro Arg Tyr Pro Gln Thr Gly Asp 260 265 270

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Ile Cys Thr Val Gly Phe Ile Ala Leu Leu Phe Thr Arg Phe Trp Leu 40

Leu Thr Val Leu Tyr Ala Ala Trp Trp Tyr Leu Asp Arg Asp Lys Pro 55

Arg Gln Gly Gly Arg His Ile Gln Ala Ile Arg Cys Trp Thr Ile Trp 75

Lys Tyr Met Lys Asp Tyr Phe Pro Ile Ser Leu Val Lys Thr Ala Glu

Leu Asp Pro Ser Arg Asn Tyr Ile Ala Gly Phe His Pro His Gly Val 100

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Tyr Val Gln Cys His Ala Pro Thr Ser Ser Ala Tyr Glu Phe Val Thr 85 90 95

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Ser Phe Trp Pro Thr Pro Ser Trp Thr His Pro Ser Ala Pro Glu Pro 625 630 630 640

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Ser Trp Pro Ala Gln Leu Pro Pro Arg Ala Pro Leu Pro Gly Lys Gly 675 680 685

Thr Arg Gly Arg Ala Glu Val Trp Thr Glu Cys Pro Ser Ser Trp 690 695 700

Ala Arg Ala Pro Arg Pro Ser Ala Pro Gly Lys 705 710 715

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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.
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Published:

- with international search report
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- (88) Date of publication of the international search report: 17 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

3

(54) Title: IN SILICO SCREENING FOR PHENOTYPE-ASSOCIATED EXPRESSED SEQUENCES

(57) Abstract: The present invention provides methods for determining whether a nucleic acid sequence is a marker for a phenotype or cell type of interest which comprises providing a database of expressed sequence tag sequences (EST's) from the species; placing said EST's in groups termed clusters based on homology of EST's within each cluster; determining for each cluster the total number of EST's within said cluster; ordering said clusters sequentially based on the number of EST's in each cluster; dividing said ordered clusters into subranges based on the number of EST's per cluster; determining for each cluster subrange obtained from step (e) the number EST's within said cluster which are expressed in said predetermined cell type of interest; calculating according to a normal distribution the number of clusters in each subrange expected to contain a predetermined threshold percentage of EST's expressed in said predetermined cell type; and identifying subranges having an observed number of clusters that meet said predetermined threshold percentage for the subrange according to normal distribution; wherein if the percentage of EST's expressed in said cell type of interest in a cluster identified is equal to or greater than said predetermined threshold percentage, the cluster contains a nucleic acid that is a marker for the cell type of interest.

INTERNATIONAL SEARCH REPORT

Int al Application No	
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C. DOCUM	MENTS CONSIDERED TO BE RELEVANT		
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	VOI. 95, January 1998 (1998-01)) names	• •
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X Furne	er documents are listed in the continuation of box C.	Patent family members are listed in	annex.
 Special cate 	egories of cited documents :		· .
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"L" document	which may throw doubts on priority claim(s) or		
citation o	or other special reason (as specified)	"Y" document of particular relevance: the elec-	nent is taken alone
O" document other me	referring to an oral disclosure use, exhibition or	document is combined with one or mose	tive step when the
P" document	published prior to the international or	ments, such combination being obvious t in the art.	o:a person skilled
	- The priority date classified	"&" document member of the same patent fam	
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	Fax: (+31-70) 340-3016	Chabros, C	
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INTERNATIONAL SEARCH REPORT

Int al Application No PCT/IB 02/04189

C.(Continua	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	PCT/IB 02/04189
Category •	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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,	SCHMITT A O ET AL: "EXHAUSTIVE MINING OF EST LIBRARIES FOR GENES DIFFERENTIALLY EXPRESSED IN NORMAL AND TUMOUR TISSUES" NUCLEIC ACIDS RESEARCH, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 27, no. 21, 1999, pages 4251-4260, XP000872807 ISSN: 0305-1048 abstract table 1	1,40,47
	page 4251, paragraph 1 - page 4253, paragraph 1	
	AUDIC S ET AL: "THE SIGNIFICANCE OF DIGITAL GENE EXPRESION PROFILES" GENOME RESEARCH, COLD SPRING HARBOR LABORATORY PRESS, US, vol. 7, 1997, pages 986-995, XP000915029 ISSN: 1088-9051 page 986 - page 989	1,40,47
		
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INTERNATIONAL SEARCH REPORT

PCT/IB 02/04189

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)	
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reason	ns:
Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:	
Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be corried by the control of the prescribed requirements to such	
an extent that no meaningful International Search can be carried out, specifically:	
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	
This International Searching Authority found multiple inventions in this international application, as follows:	
see additional sheet	
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.	
2. As all searchable claims could be convoled with a convoled	
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.	į
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:	
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:	
1-21,40-55	
Remark on Protest The additional search fees were accompanied by the applicant's protest.	
No protest accompanied the payment of additional search fees.	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims: 1-21,40-55

relates to a method for determining nucleic acid markers for a predetermined phenotype or cell type of interest, consisting of algorithmic steps.

Independent claims 40 and 47 define embodiments of independent claim 1.

Inventions 2-202: claims 22-39 (all partially)

relate to nucleic acid sequences identified by SEQ ID NOs 9-141, cited in claim 24, and corresponding amino acid sequences, cited in claim 29.

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